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Method M
Monoclonal Purified

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CAUTION: US Federal law prohibits dispensing without prescription.

HOW SUPPLIED

Immune Globulin Intravenous (Human), Panglobulin™, is available as a white lyophilized powder in 6 and 12 g size vials. The only diluents which may be used to reconstitute the product are sterile (0.9%) Sodium Chloride Injection USP, 5% Dextrose, or Sterile Water.

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(HUMAN)

HOW SUPPLIED

Immune Globulin Intravenous (Human), Polygam® S/D, is supplied in 2.5 g, 5 g or 10 g single use bottles. Each bottle of Immune Globulin Intravenous (Human), Polygam® S/D, is furnished with a suitable volume of Sterile Water for Injection, USP, a transfer device and an administration set which contains an integral airway and a 15 micron filter.

2.5g NDC 52769-471-72
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Amgen

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EPOGEN® ℞
EPOETIN ALFA
RECOMBINANT
For Injection

DESCRIPTION

Erythropoietin is a glycoprotein which stimulates red blood cell production. It is produced in the kidney and stimulates the division and differentiation of committed erythroid progenitors in the bone marrow. EPOGEN® (Epoetin alfa), a 165 amino acid glycoprotein manufactured by recombinant DNA technology, has the same biological effects as endogenous erythropoietin.[1] It has a molecular weight of 30,400 daltons and is produced by mammalian cells into which the human erythropoietin gene has been introduced. The product contains the identical amino acid sequence of isolated natural erythropoietin.

EPOGEN® is formulated as a sterile, colorless liquid in an isotonic sodium chloride/sodium citrate buffered solution for intravenous (IV) or subcutaneous (SC) administration.

Single-dose, Preservative-free Vial: Each 1 mL of solution contains 2000, 3000, 4000 or 10,000 Units of Epoetin alfa, 2.5 mg Albumin (Human), 5.8 mg sodium citrate, 5.8 mg sodium chloride, and 0.06 mg citric acid in Water for Injection, USP (pH 6.9 ± 0.3). This formulation contains no preservative.

Multidose, Preserved Vial: 2 mL (20,000 Units, 10,000 Units/mL). Each 1 mL of solution contains 10,000 Units of Epoetin alfa, 2.5 mg Albumin (Human), 1.3 mg sodium citrate, 8.2 mg sodium chloride, 0.11 mg citric acid, and 1% benzyl alcohol as preservative in Water for Injection, USP (pH 6.1 ± 0.3).

Multidose, Preserved Vial: 1 mL (20,000 Units/mL). Each 1 mL of solution contains 20,000 Units of Epoetin alfa, 2.5 mg Albumin (Human), 1.3 mg sodium citrate, 8.2 mg sodium chloride, 0.11 mg citric acid, and 1% benzyl alcohol as preservative in Water for Injection, USP (pH 6.1 ± 0.3).

CLINICAL PHARMACOLOGY

Chronic Renal Failure Patients

Endogenous production of erythropoietin is normally regulated by the level of tissue oxygenation. Hypoxia and anemia generally increase the production of erythropoietin, which in turn stimulates erythropoiesis.[2] In normal subjects, plasma erythropoietin levels range from 0.01 to 0.03 Units/mL and increase up to 100- to 1000-fold during hypoxia or anemia.[2,3] In contrast, in patients with chronic renal failure (CRF), production of erythropoietin is impaired, and this erythropoietin deficiency is the primary cause of their anemia.[3,4]

Chronic renal failure is the clinical situation in which there is a progressive and usually irreversible decline in kidney function. Such patients may manifest the sequelae of renal dysfunction, including anemia, but do not necessarily require regular dialysis. Patients with end-stage renal disease (ESRD) are those patients with CRF who require regular dialysis or kidney transplantation for survival.

EPOGEN® has been shown to stimulate erythropoiesis in anemic patients with CRF, including both patients on dialysis and those who do not require regular dialysis.[4-12] The first evidence of a response to the three times weekly (TIW) administration of EPOGEN® is an increase in the reticulocyte count within 10 days, followed by increases in the red cell count, hemoglobin, and hematocrit, usually within 2 to 6 weeks.[4,8] Because of the length of time required for erythropoiesis—several days for erythroid progenitors to mature and be released into the circulation—a clinically significant increase in hematocrit is usually not observed in less than 2 weeks and may require up to 6 weeks in some patients. Once the hematocrit reaches the suggested target range (30% to 36%), that level can be sustained by EPOGEN® therapy in the absence of iron deficiency and concurrent illnesses.

The rate of hematocrit increase varies between patients and is dependent upon the dose of EPOGEN®, within a therapeutic range of approximately 50 to 300 Units/kg TIW.[4] A greater biologic response is not observed at doses exceeding 300 Units/kg TIW.[4] Other factors affecting the rate and extent of response include availability of iron stores, the baseline hematocrit, and the presence of concurrent medical problems.

Zidovudine-treated HIV-infected Patients

Responsiveness to EPOGEN® in HIV-infected patients is dependent upon the endogenous serum erythropoietin level prior to treatment. Patients with endogenous serum erythropoietin levels ≤500 mUnits/mL, and who are receiving a dose of zidovudine ≤4200 mg/week, may respond to EPOGEN® therapy. Patients with endogenous serum erythropoietin levels >500 mUnits/mL do not appear to respond to EPOGEN® therapy. In a series of four clinical trials involving 255 patients, 60% to 80% of HIV-infected patients treated with zidovudine had endogenous serum erythropoietin levels ≤500 mUnits/mL.

Response to EPOGEN® in zidovudine-treated HIV-infected patients is manifested by reduced transfusion requirements and increased hematocrit.

Cancer Patients on Chemotherapy

Anemia in cancer patients may be related to the disease itself or the effect of concomitantly administered chemotherapeutic agents. EPOGEN® has been shown to increase hematocrit and decrease transfusion requirements after the first month of therapy (months 2 and 3), in anemic cancer patients undergoing chemotherapy.

A series of clinical trials enrolled 131 anemic cancer patients who were receiving cyclic cisplatin- or non cisplatin-containing chemotherapy. Endogenous baseline serum erythropoietin levels varied among patients in these trials with approximately 75% (n=83/110) having endogeneous serum erythropoietin levels ≤132 mUnits/mL, and approximately 4% (n=4/110) of patients having endogenous serum erythropoietin levels >500 mUnits/mL. In general, patients with lower baseline serum erythropoietin levels responded more vigorously to EPOGEN® than patients with higher baseline erythropoietin levels. Although no specific serum erythropoietin level can be stipulated above which patients would be unlikely to respond to EPOGEN® therapy, treatment of patients with grossly elevated serum erythropoietin levels (eg, >200 mUnits/mL) is not recommended.

Pharmacokinetics

Intravenously administered EPOGEN® is eliminated at a rate consistent with first order kinetics with a circulating half-life ranging from approximately 4 to 13 hours in patients with CRF. Within the therapeutic dose range, detectable levels of plasma erythropoietin are maintained for at least 24 hours.[7] After SC administration of EPOGEN® to patients with CRF, peak serum levels are achieved within 5 to 24 hours after administration and decline slowly thereafter. There is no apparent difference in half-life between patients not on dialysis whose serum creatinine levels were greater than 3, and patients maintained on dialysis.

In normal volunteers, the half-life of IV administered EPOGEN® is approximately 20% shorter than the half-life in CRF patients. The pharmacokinetics of EPOGEN® have not been studied in HIV-infected patients.

INDICATIONS AND USAGE

Treatment of Anemia of Chronic Renal Failure Patients

EPOGEN® is indicated for the treatment of anemia associated with CRF, including patients on dialysis (ESRD) and patients not on dialysis. EPOGEN® is indicated to elevate or maintain the red blood cell level (as manifested by the hematocrit or hemoglobin determinations) and to decrease the need for transfusions in these patients.

Non-dialysis patients with symptomatic anemia considered for therapy should have a hematocrit less than 30%.

EPOGEN® is not intended for patients who require immediate correction of severe anemia. EPOGEN® may obviate the need for maintenance transfusions but is not a substitute for emergency transfusion.

Prior to initiation of therapy, the patient's iron stores should be evaluated. Transferrin saturation should be at least 20% and ferritin at least 100 ng/mL. Blood pressure should be adequately controlled prior to initiation of EPOGEN® therapy, and must be closely monitored and controlled during therapy.

EPOGEN® should be administered under the guidance of a qualified physician (see DOSAGE AND ADMINISTRATION).

Treatment of Anemia in Zidovudine-treated HIV-Infected Patients

EPOGEN® is indicated for the treatment of anemia related to therapy with zidovudine in HIV-infected patients. EPOGEN® is indicated to elevate or maintain the red blood cell level (as manifested by the hematocrit or hemoglobin determinations) and to decrease the need for transfusions in these patients. EPOGEN® is not indicated for the treatment of anemia in HIV-infected patients due to other factors such as iron or folate deficiencies, hemolysis or gastrointestinal bleeding, which should be managed appropriately.

EPOGEN®, at a dose of 100 Units/kg TIW, is effective in decreasing the transfusion requirement and increasing the red blood cell level of anemic, HIV-infected patients treated with zidovudine, when the endogenous serum erythropoietin level is ≤500 mUnits/mL and when patients are receiving a dose of zidovudine ≤4200 mg/week.

Treatment of Anemia in Cancer Patients on Chemotherapy

EPOGEN® is indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy. EPOGEN® is indicated to decrease the need for transfusions in patients who will be receiving concomitant chemotherapy for a minimum of 2 months. EPOGEN is not indicated for the treatment of anemia in cancer patients due to other factors such as iron or folate deficiencies, hemolysis or gastrointestinal bleeding which should be managed appropriately.

Reduction of Allogeneic Blood Transfusion in Surgery Patients

EPOGEN® is indicated for the treatment of anemic patients (hemoglobin >10 to ≤ 13 g/dL) scheduled to undergo elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusions.[14-16] EPOGEN® is indicated for patients at high risk for perioperative transfusions with significant, anticipated blood loss. EPOGEN® is not indicated for anemic patients who are willing to donate autologous blood. The safety of the perioperative use of EPOGEN® has been studied only in patients who are receiving anticoagulant prophylaxis.

CLINICAL EXPERIENCE: RESPONSE TO EPOGEN®

Chronic Renal Failure Patients

Response to EPOGEN® was consistent across all studies. In the presence of adequate iron stores (see IRON EVALUATION), the time to reach the target hematocrit is a function of the baseline hematocrit and the rate of hematocrit rise. The rate of increase in hematocrit is dependent upon the dose of EPOGEN® administered and individual patient

Continued on next page

Epogen—Cont.

variation. In clinical trials at starting doses of 50 to 150 Units/kg TIW, patients responded with an average rate of hematocrit rise of:

STARTING DOSE (TIW IV)	HEMATOCRIT INCREASE POINTS/DAY	POINTS/2 WEEKS
50 Units/kg	0.11	1.5
100 Units/kg	0.18	2.5
150 Units/kg	0.25	3.5

Over this dose range, approximately 95% of all patients responded with a clinically significant increase in hematocrit, and by the end of approximately 2 months of therapy virtually all patients were transfusion-independent. Changes in the quality of life of patients treated with EPOGEN® were assessed as part of a Phase 3 clinical trial.[5,6] Once the target hematocrit (32% to 38%) was achieved, statistically significant improvements were demonstrated for most quality of life parameters measured, including energy and activity level, functional ability, sleep and eating behavior, health status, satisfaction with health, sex life, well-being, psychological effect, life satisfaction, and happiness. Patients also reported improvement in their disease symptoms. They showed a statistically significant increase in exercise capacity (VO_2 max), energy, and strength with a significant reduction in aching, dizziness, anxiety, shortness of breath, muscle weakness, and leg cramps.[6,17]

Patients on Dialysis

Thirteen clinical studies were conducted, involving IV administration to a total of 1010 anemic patients on dialysis for 986 patient-years of EPOGEN® therapy. In the three largest of these clinical trials, the median maintenance dose necessary to maintain the hematocrit between 30% to 36% was approximately 75 Units/kg TIW. In the US multicenter Phase 3 study, approximately 65% of the patients required doses of 100 Units/kg TIW, or less, to maintain their hematocrit at approximately 35%. Almost 10% of patients required a dose of 25 Units/kg, or less, and approximately 10% required a dose of more than 200 Units/kg TIW to maintain their hematocrit at this level.

A multicenter unit dose study was also conducted in 119 patients receiving peritoneal dialysis who self-administered EPOGEN® subcutaneously for approximately 109 patient-years of experience. Patients responded to EPOGEN® administered SC in a manner similar to patients receiving IV administration.[18]

Patients with CRF Not Requiring Dialysis

Four clinical trials were conducted in patients with CRF not on dialysis involving 181 patients treated with EPOGEN® for approximately 67 patient-years of experience. These patients responded to EPOGEN® therapy in a manner similar to that observed in patietns on dialysis. Patients with CRF not on dialysis demonstrated a dose-dependent and sustained increase in hematocrit when EPOGEN® was administered by either an IV or SC route, with similar rates of rise of hematocrit when EPOGEN® was administered by either route. Moreover, EPOGEN® doses of 75 to 150 Units/kg per week have been shown to maintain hematocrits of 36% to 38% for up to 6 months. Correcting the anemia of progressive renal failure will allow patients to remain active even though their renal function continues to decrease.[19-21]

Zidovudine-treated HIV-Infected Patients

EPOGEN® has been studied in four placebo-controlled trials enrolling 297 anemic (hematocrit < 30%) HIV-infected (AIDS) patients receiving concomitant therapy with zidovudine (all patients were treated with Epoetin alfa manufactured by Amgen Inc.). In the subgroup of patients (89/125 EPOGEN® and 58/130 placebo) with prestudy endogenous serum erythropoietin levels ≤ 500 mUnits/mL, EPOGEN® reduced the mean cumulative number of units of blood transfused per patient by approximately 40% as compared to the placebo group.[22] Among those patients who required transfusions at baseline, 43% of patients treated with EPOGEN® versus 18% of placebo-treated patients were transfusion-independent during the second and third months of therapy. EPOGEN® therapy also resulted in significant increases in hematocrit in comparison to placebo. When examining the results according to the weekly dose of zidovudine received during month 3 of therapy, there was a statistically significant ($p < 0.003$) reduction in transfusion requirements in patients treated with EPOGEN® (n = 51) compared to placebo treated patients (n = 54) whose mean weekly zidovudine dose was ≤ 4200 mg/week.[22]

Approximately 17% of the patients with endogenous serum erythropoietin levels ≤ 500 mUnits/mL receiving EPOGEN® in doses from 100 to 200 Units/kg TIW achieved a hematocrit of 38% without administration of transfusions or significant reduction in zidovudine dose. In the subgroup of patients whose prestudy endogenous serum erythropoietin levels were > 500 mUnits/mL, EPOGEN® therapy did not reduce transfusion requirements or increase hematocrit, compared to the corresponding responses in placebo-treated patients. In a six month open-label EPOGEN® study, patients responded with decreased transfusion requirements and sustained increases in hematocrit and hemoglobin with doses of EPOGEN® up to 300 Units/kg TIW.[21-23]

Responsiveness to EPOGEN® therapy may be blunted by intercurrent infectious/inflammatory episodes and by an increase in zidovudine dosage. Consequently, the dose of EPOGEN® should be titrated to maintain adequate hematocrit.

Cancer Patients on Chemotherapy

EPOGEN® has been studied in a series of placebo-controlled, double-blind trials in a total of 131 anemic cancer patients. Within this group, 72 patients were treated with concomitant non cisplatin-containing chemotherapy regimens and 59 patients were treated with concomitant cisplatin-containing chemotherapy regimens. Patients were randomized to EPOGEN® 150 Units/kg or placebo subcutaneously TIW for 12 weeks.

EPOGEN® therapy was associated with a significantly ($p < 0.008$) greater hematocrit response than in the corresponding placebo-treated patients (see table).[22]

STUDY	HEMATOCRIT (%): MEAN CHANGE FROM BASELINE TO FINAL VALUE* EPOGEN®	PLACEBO
Chemotherapy	7.6	1.3
Cisplatin	6.9	0.6

* Significantly higher in EPOGEN® patients than in placebo patients ($p<0.008$)

In the two types of chemotherapy studies (utilizing an EPOGEN® dose of 150 Units/kg TIW), the mean number of units of blood transfused per patient after the first month of therapy was significantly ($p < 0.02$) lower in patients treated with EPOGEN® (0.71 units in months 2, 3) than in corresponding placebo-treated patients (1.84 units in months 2, 3). Moreover, the proportion of patients transfused during months 2 and 3 of therapy combined was significantly ($p < 0.03$) lower in the patients treated with EPOGEN® than in the corresponding placebo-treated patients (22% vs 43%).[22]

Comparable intensity of chemotherapy in the EPOGEN® and placebo groups in the chemotherapy trials was suggested by a similar area under the neutrophil time curve in patients treated with EPOGEN® and placebo-treated patients as well as by a similar proportion of patients in groups treated with EPOGEN® and placebo-treated groups whose absolute neutrophil counts fell below 1000 cells/μL. Available evidence suggests that patients with lymphoid and solid cancers respond equivalently to EPOGEN® therapy, and that patients with or without tumor infiltration of the bone marrow respond equivalently to EPOGEN® therapy.

Surgery Patients

EPOGEN® has been studied in a placebo-controlled, double-blind trial enrolling 316 patients scheduled for major, elective orthopedic hip or knee surgery who were expected to require ≥ 2 units of blood and who were not able or willing to participate in an autologous blood donation program. Based on previous studies which demonstrated that pretreatment hemoglobin is a predictor of risk of receiving transfusion,[16,24] patients were stratified into one of three groups based on their pretreatment hemoglobin [≤ 10 (n = 2), > 10 to ≤ 13 (n = 96), and > 13 to ≤ 15 g/dL (n = 218)] and then randomly assigned to receive 300 Units/kg EPOGEN®, 100 Units/kg EPOGEN® or placebo by SC injection for 10 days before surgery, on the day of surgery, and for four days after surgery.[14] All patients received oral iron and a low-dose post-operative warfarin regimen.[14]

Treatment with EPOGEN® 300 Units/kg significantly ($p = 0.024$) reduced the risk of allogeneic transfusion in patients with a pretreatment hemoglobin of > 10 to ≤ 13 g/dL; 5/31 (16%) of EPOGEN® 300 Units/kg, 6/26 (23%) of EPOGEN® 100 Units/kg, and 13/29 (45%) of placebo-treated patients were transfused.[14] There was no significant difference in the number of patients transfused between EPOGEN® (9% 300 Units/kg, 6% 100 Units/kg) and placebo (13%) in the > 13 to ≤ 15 g/dL hemoglobin stratum. There were too few patients in the ≤ 10 g/dL group to determine if EPOGEN® is useful in this hemoglobin strata. In the > 10 to ≤ 13 g/dL pretreatment stratum, the mean number of units transfused per EPOGEN® treated patient (0.45 units blood for 300 Units/kg, 0.42 units blood for 100 Units/kg) was less than the mean transfused per placebo-treated patient (1.14 units) (overall $p = 0.028$). In addition, mean hemoglobin, hematocrit and reticulocyte counts increased significantly during the presurgery period in patients treated with EPOGEN®.[14]

EPOGEN® was also studied in an open-label, parallel-group trial enrolling 145 subjects with a pretreatment hemoglobin level of ≥ 10 to ≤ 13 g/dL who were scheduled for major orthopedic hip or knee surgery and who were not participating in an autologous program.[15] Subjects were randomly assigned to receive one of two SC dosing regimens of EPOGEN® (600 Units/kg once weekly for three weeks prior to surgery and on the day of surgery, or 300 Units/kg once daily for 10 days prior to surgery, on the day of surgery and for 4 days after surgery). All subjects received oral iron and appropriate pharmacologic anticoagulation therapy.

From pretreatment to presurgery, the mean increase in hemoglobin in the 600 Units/kg weekly group (1.44 g/dL) was greater than observed in the 300 Units/kg daily group.[15] The mean increase in absolute reticulocyte count was smaller in the weekly group ($0.11 \times 10^6/mm^3$) compared to the daily group ($0.17 \times 10^6/mm^3$). Mean hemoglobin levels were similar for the two treatment groups throughout the postsurgical period.

The erythropoietic response observed in both treatment Units/kg daily group].[15] The mean number of units transfused per subject was approximately 0.3 units in both treatment groups.

CONTRAINDICATIONS

EPOGEN® is contraindicated in patients with:

1. Uncontrolled hypertension.
2. Known hypersensitivity to mammalian cell-derived products.
3. Known hypersensitivity to Albumin (Human).

WARNINGS

Pediatric Use

The multidose preserved formulation contains benzyl alcohol. Benzyl alcohol has been reported to be associated with an increased incidence of neurological and other complications in premature infants which are sometimes fatal. The safety and effectiveness of Epoetin alfa in pediatric patients have not been established.

Thrombotic Events and Increased Mortality

A randomized, prospective trial of 1265 hemodialysis patients with clinically evident cardiac disease (ischemic heart disease or congestive heart failure) was conducted in which patients were assigned to EPOGEN® treatment targeted to a maintenance hematocrit of either 42 ± 3% or 30 ± 3%. Increased mortality was observed in 634 patients randomized to a target hematocrit of 42% [221 deaths (35% mortality)] compared to 631 patients targeted to remain at a hematocrit of 30% [185 deaths (29% mortality)]. The reasons for the increased mortality observed in these studies is unknown, however the incidence of non-fatal myocardial infarctions (3.1% vs 2.3%), vascular access thromboses (39% vs 29%), and all other thrombotic events (22% vs 18%) were also higher in the group randomized to achieve a hematocrit of 42%.

Increased mortality was also observed in a randomized placebo-controlled study of EPOGEN® in patients who did not have CRF who were undergoing coronary artery bypass surgery (7 deaths in 126 patients randomized to EPOGEN® versus no deaths among 56 patients receiving placebo). Four of these deaths occurred during the period of study drug administration and all 4 deaths were associated with thrombotic events. While the extent of the population affected is unknown, in patients at risk for thrombosis, the anticipated benefits of EPOGEN® treatment should be weighed against the potential for increased risks associated with therapy.

Chronic Renal Failure Patients

Hypertension: Patients with uncontrolled hypertension should not be treated with EPOGEN®; blood pressure should be controlled adequately before initiation of therapy. Up to 80% of patients with CRF have a history of hypertension.[25] Although there does not appear to be any direct pressor effects of EPOGEN®, blood pressure may rise during EPOGEN® therapy. During the early phase of treatment when the hematocrit is increasing, approximately 25% of patients on dialysis may require initiation of, or increase in, antihypertensive therapy. Hypertensive encephalopathy and seizures have been observed in patients with CRF treated with EPOGEN®.

Special care should be taken to closely monitor and aggressively control blood pressure in patients treated with EPOGEN®. Patients should be advised as to the importance of compliance with antihypertensive therapy and dietary restrictions. If blood pressure is difficult to control by initiation of appropriate measures, the hematocrit may be reduced by decreasing or withholding the dose of EPOGEN®. A clinically significant decrease in hematocrit may not be observed for several weeks.

It is recommended that the dose of EPOGEN® be decreased if the hematocrit increase exceeds 4 points in any 2-week period, because of the possible association of excessive rate of rise of hematocrit with an exacerbation of hypertension. In CRF patients on hemodialysis with clinically evident ischemic heart disease or congestive heart failure, the hematocrit should be managed carefully, not to exceed 36% (SEE THROMBOTIC EVENTS).

Seizures: Seizures have occurred in patients with CRF participating in EPOGEN® clinical trials.

In patients on dialysis, there was a higher incidence of seizures during the first 90 days of therapy (occurring in approximately 2.5% of patients) as compared with later time points.

Given the potential for an increased risk of seizures during the first 90 days of therapy, blood pressure and the presence of premonitory neurologic symptoms should be monitored closely. Patients should be cautioned to avoid potentially hazardous activities such as driving or operating heavy machinery during this period.

While the relationship between seizures and the rate of rise of hematocrit is uncertain, it is recommended that the dose of EPOGEN® be decreased if the hematocrit increase exceeds 4 points in any 2-week period.

Thrombotic Events: During hemodialysis, patients treated with EPOGEN® may require increased anticoagulation with heparin to prevent clotting of the artificial kidney (see ADVERSE REACTIONS for more information about thrombotic events).

Other thrombotic events (eg, myocardial infarction, cerebrovascular accident, transient ischemic attack) have occurred in clinical trials at an annualized rate of less than 0.1 events per patient per year of EPOGEN® therapy. The trials were conducted in patients with CRF (whether on dialysis or not) in whom the target hematocrit was 32%

...ients with ischemic heart disease or congestive heart failure receiving EPOGEN® therapy with the goal of reaching a normal hematocrit (42%) as compared to a target hematocrit of 30%. Patients with pre-existing cardiovascular disease should be monitored closely.

Zidovudine-treated HIV-Infected Patients

In contrast to CRF patients, EPOGEN® therapy has not been linked to exacerbation of hypertension, seizures, and thrombotic events in HIV-infected patients.

PRECAUTIONS

The parenteral administration of any biologic product should be attended by appropriate precautions in case allergic or other untoward reactions occur (see CONTRAINDICATIONS). In clinical trials, while transient rashes were occasionally observed concurrently with EPOGEN® therapy, no serious allergic or anaphylactic reactions were reported (see ADVERSE REACTIONS for more information regarding allergic reactions).

The safety and efficacy of EPOGEN® therapy have not been established in patients with a known history of a seizure disorder or underlying hematologic disease (eg, sickle cell anemia, myelodysplastic syndromes, or hypercoagulable disorders).

In some female patients, menses have resumed following EPOGEN® therapy; the possibility of pregnancy should be discussed and the need for contraception evaluated.

Hematology

Exacerbation of porphyria has been observed rarely in patients with CRF treated with EPOGEN®. However, EPOGEN® has not caused increased urinary excretion of porphyrin metabolites in normal volunteers, even in the presence of a rapid erythropoietic response. Nevertheless, EPOGEN® should be used with caution in patients with known porphyria.

In preclinical studies in dogs and rats, but not in monkeys, EPOGEN® therapy was associated with subclinical bone marrow fibrosis. Bone marrow fibrosis is a known complication of CRF in humans and may be related to secondary hyperparathyroidism or unknown factors. The incidence of bone marrow fibrosis was not increased in a study of patients on dialysis who were treated with EPOGEN® for 12 to 19 months, compared to the incidence of bone marrow fibrosis in a matched group of patients who had not been treated with EPOGEN®.

Hematocrit in CRF patients should be measured twice a week; zidovudine-treated HIV-infected and cancer patients should have hematocrit measured once a week until hematocrit has been stabilized, and measured periodically thereafter.

Delayed or Diminished Response

If the patient fails to respond or to maintain a response to doses within the recommended dosing range, the following etiologies should be considered and evaluated:

1. Iron deficiency: Virtually all patients will eventually require supplemental iron therapy (see IRON EVALUATION).
2. Underlying infectious, inflammatory, or malignant processes.
3. Occult blood loss.
4. Underlying hematologic diseases (ie, thalassemia, refractory anemia, or other myelodysplastic disorders).
5. Vitamin deficiencies: Folic acid or vitamin B12.
6. Hemolysis.
7. Aluminum intoxication.
8. Osteitis fibrosa cystica.

Iron Evaluation

During EPOGEN® therapy, absolute or functional iron deficiency may develop. Functional iron deficiency, with normal ferritin levels but low transferrin saturation, is presumably due to the inability to mobilize iron stores rapidly enough to support increased erythropoiesis. Transferrin saturation should be at least 20% and ferritin should be at least 100 ng/mL.

Prior to and during EPOGEN® therapy, the patient's iron status, including transferrin saturation (serum iron divided by iron binding capacity) and serum ferritin, should be evaluated. Virtually all patients will eventually require supplemental iron to increase or maintain transferrin saturation to levels which will adequately support erythropoiesis stimulated by EPOGEN®. All surgery patients being treated with EPOGEN® should receive adequate iron supplementation throughout the course of therapy in order to support erythropoiesis and avoid depletion of iron stores.

Drug Interaction

No evidence of interaction of EPOGEN® with other drugs was observed in the course of clinical trials.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenic potential of EPOGEN® has not been evaluated. EPOGEN® does not induce bacterial gene mutation (Ames Test), chromosomal aberrations in mammalian cells, micronuclei in mice, or gene mutation at the HGPRT locus. In female rats treated IV with EPOGEN®, there was a trend for slightly increased fetal wastage at doses of 100 and 500 Units/kg.

Pregnancy Category C

EPOGEN® has been shown to have adverse effects in rats when given in doses 5 times the human dose. There are no adequate and well-controlled studies in pregnant women. EPOGEN® should be used during pregnancy only if potential benefit justifies the potential risk to the fetus.

In studies of female rats, there were decreases in body weight gain, delays in appearance of abdominal hair, delayed eyelid opening, delayed ossification, and decreases in the number of caudal vertebrae in the F1 fetuses of the 500 Units/kg group. In female rats treated IV, there was a trend for slightly increased fetal wastage at dosages of 100 and 500 Units/kg. EPOGEN® has not shown any adverse effect at doses as high as 500 Units/kg in pregnant rabbits (from day 6 to 18 of gestation).

Nursing Mothers

Postnatal observations of the live offspring (F1 generation) of female rats treated with EPOGEN® during gestation and lactation revealed no effect of EPOGEN® at doses of up to 500 Units/kg. There were, however, decreases in body weight gain, delays in appearance of abdominal hair, eyelid opening, and decreases in the number of caudal vertebrae in the F1 fetuses of the 500 Units/kg group. There were no EPOGEN®-related effects on the F2 generation fetuses.

It is not known whether EPOGEN® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when EPOGEN® is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of EPOGEN® in pediatric patients have not been established (see WARNINGS).

Chronic Renal Failure Patients

Patients with CRF Not Requiring Dialysis

Blood pressure and hematocrit should be monitored no less frequently than for patients maintained on dialysis. Renal function and fluid and electrolyte balance should be closely monitored, as an improved sense of well-being may obscure the need to initiate dialysis in some patients.

Hematology: Sufficient time should be allowed to determine a patient's responsiveness to a dosage of EPOGEN® before adjusting the dose. Because of the time required for erythropoiesis and the red cell half-life, an interval of 2 to 6 weeks may occur between the time of a dose adjustment (initiation, increase, decrease, or discontinuation) and a significant change in hematocrit.

In order to avoid reaching the suggested target hematocrit too rapidly, or exceeding the suggested target range (hematocrit of 30% to 36%), the guidelines for dose and frequency of dose adjustments (see DOSAGE AND ADMINISTRATION) should be followed.

For patients who respond to EPOGEN® with a rapid increase in hematocrit (eg, more than 4 points in any 2-week period), the dose of EPOGEN® should be reduced because of the possible association of excessive rate of rise of hematocrit with an exacerbation of hypertension.

The elevated bleeding time characteristic of CRF decreases toward normal after correction of anemia in patients treated with EPOGEN®. Reduction of bleeding time also occurs after correction of anemia by transfusion.

Laboratory Monitoring: The hematocrit should be determined twice a week until it has stabilized in the suggested target range and the maintenance dose has been established. After any dose adjustment, the hematocrit should also be determined twice weekly for at least 2 to 6 weeks until it has been determined that the hematocrit has stabilized in response to the dose change. The hematocrit should then be monitored at regular intervals.

A complete blood count with differential and platelet count should be performed regularly. During clinical trials, modest increases were seen in platelets and white blood cell counts. While these changes were statistically significant, they were not clinically significant and the values remained within normal ranges.

In patients with CRF, serum chemistry values (including blood urea nitrogen (BUN), uric acid, creatinine, phosphorus, and potassium) should be monitored regularly. During clinical trials in patients on dialysis, modest increases were seen in BUN, creatinine, phosphorus, and potassium. In some patients with CRF not on dialysis, treated with EPOGEN®, modest increases in serum uric acid and phosphorus were observed. While changes were statistically significant, the values remained within the ranges normally seen in patients with CRF.

Diet: As the hematocrit increases and patients experience an improved sense of well-being and quality of life, the importance of compliance with dietary and dialysis prescriptions should be reinforced. In particular, hyperkalemia is not uncommon in patients with CRF. In US studies in patients on dialysis, hyperkalemia has occurred at an annualized rate of approximately 0.11 episodes per patient-year of EPOGEN® therapy, often in association with poor compliance to medication, diet, and/or dialysis.

Dialysis Management: Therapy with EPOGEN® results in an increase in hematocrit and a decrease in plasma volume which could affect dialysis efficiency. In studies to date, the resulting increase in hematocrit did not appear to adversely affect dialyzer function[9,10] or the efficiency of high flux hemodialysis.[11] During hemodialysis, patients treated with EPOGEN® may require increased anticoagulation with heparin to prevent clotting of the artificial kidney.

Patients who are marginally dialyzed may require adjustments in their dialysis prescription. As with all patients on dialysis, the serum chemistry values (including BUN, creatinine, phosphorus, and potassium) in patients treated with EPOGEN® should be monitored regularly to assure the adequacy of the dialysis prescription.

Information for Patients: In those situations in which the physician determines that a home dialysis patient can safely and effectively self-administer EPOGEN®, the patient should be instructed as to the proper dosage and administration. Home dialysis patients should be referred to the full "Information for Home Dialysis Patients" insert; it is not a disclosure of all possible effects. Patients should be informed of the signs and symptoms of allergic drug reaction and advised of appropriate actions. If home use is prescribed for a home dialysis patient, the patient should be thoroughly instructed in the importance of proper disposal and cautioned against the reuse of needles, syringes and drug product. A puncture-resistant container for the disposal of used syringes and needles should be available to the patient. The full container should be disposed of, according to the directions provided by the physician.

Renal Function: In patients with CRF not on dialysis, renal function and fluid and electrolyte balance should be closely monitored, as an improved sense of well-being may obscure the need to initiate dialysis in some patients. In patients with CRF not on dialysis, placebo-controlled studies of progression of renal dysfunction over periods of greater than one year have not been completed. In shorter term trials in patients with CRF not on dialysis, changes in creatinine and creatinine clearance were not significantly different in patients treated with EPOGEN®, compared with placebo-treated patients. Analysis of the slope of 1/serum creatinine versus time plots in these patients indicates no significant change in the slope after the initiation of EPOGEN® therapy.

Zidovudine-treated HIV-Infected Patients

Hypertension: Exacerbation of hypertension has not been observed in zidovudine-treated HIV-infected patients treated with EPOGEN®. However, EPOGEN® should be withheld in these patients if pre-existing hypertension is uncontrolled, and should not be started until blood pressure is controlled. In double-blind studies, a single seizure has been experienced by a patient treated with EPOGEN®.

Cancer Patients on Chemotherapy

Hypertension: Hypertension, associated with a significant increase in hematocrit, has been noted rarely in patients treated with EPOGEN®. Nevertheless, blood pressure in patients treated with EPOGEN® should be monitored carefully, particularly in patients with an underlying history of hypertension or cardiovascular disease.

Seizures: In double-blind, placebo-controlled trials, 3.2% (n=2/63) of patients treated with EPOGEN® and 2.9% (n=2/68) of placebo-treated patients had seizures. Seizures in 1.6% (n=1/63) of patients treated with EPOGEN® occurred in the context of a significant increase in blood pressure and hematocrit from baseline values. However, both patients treated with EPOGEN® also had underlying CNS pathology which may have been related to seizure activity.

Thrombotic Events: In double-blind, placebo-controlled trials, 3.2% (n=2/63) of patients treated with EPOGEN® and 11.8% (n=8/68) of placebo-treated patients had thrombotic events (eg, pulmonary embolism, cerebrovascular accident).

Growth Factor Potential: EPOGEN® is a growth factor that primarily stimulates red cell production. However, the possibility that EPOGEN® can act as a growth factor for any tumor type, particularly myeloid malignancies, cannot be excluded.

Surgery patients

Thrombotic/Vascular Events: In perioperative clinical trials with orthopedic patients, the overall incidence of thrombotic/vascular events was similar in Epoetin alfa and placebo-treated patients who had a pretreatment hemoglobin of >10 to ≤13 g/dL. In patients with a hemoglobin of >13 g/dL treated with 300 Units/kg of Epoetin alfa, the possibility that EPOGEN® treatment may be associated with an increased risk of postoperative thrombotic/vascular events cannot be excluded.[14-16]

In one study in which Epoetin alfa was administered in the perioperative period to patients undergoing coronary artery bypass graft surgery, there were seven deaths in the group treated with Epoetin alfa (n=126) and no deaths in the placebo-treated group (n=56). Among the seven deaths in the patients treated with Epoetin alfa, four were at the time of therapy (between study day 2 and 8). The four deaths at the time of therapy (3%) were associated with thrombotic/vascular events. A causative role of Epoetin alfa cannot be excluded (see WARNINGS).

Hypertension: Blood pressure may rise in the perioperative period in patients being treated with EPOGEN®. Therefore, blood pressure should be monitored carefully.

ADVERSE REACTIONS

Chronic Renal Failure Patients

EPOGEN® is generally well-tolerated. The adverse events reported are frequent sequelae of CRF and are not necessarily attributable to EPOGEN® therapy. In double-blind, placebo-controlled studies involving over 300 patients with CRF, the events reported in greater than 5% of patients treated with EPOGEN® during the blinded phase were:

PERCENT OF PATIENTS REPORTING EVENT

Event	Patients Treated with EPOGEN® (n = 200)	Placebo-Treated Patients (n =135)
Hypertension	24%	19%
Headache	16%	12%
Arthralgias	11%	6%
Nausea	11%	9%
Edema	9%	10%
Fatigue	9%	14%
Diarrhea	9%	6%
Vomiting	8%	5%
Chest Pain	7%	9%
Skin Reaction, Administration Site	7%	12%

Continued on next page

Epogen—Cont.

Asthenia	7%	12%
Dizziness	7%	13%
Clotted Access	7%	2%

Significant adverse events of concern in patients with CRF treated in double-blind, placebo-controlled trials occurred in the following percent of patients during the blinded phase of the studies:

Seizure	1.1%	1.1%
CVA/TIA	0.4%	0.6%
MI	0.4%	1.1%
Death	0%	1.7%

In the US EPOGEN® studies in patients on dialysis (over 567 patients), the incidence (number of events per patient-year) of the most frequently reported adverse events were hypertension (0.75), headache (0.40), tachycardia (0.31), nausea/vomiting (0.26), clotted vascular access (0.25), shortness of breath (0.14), hyperkalemia (0.11), and diarrhea (0.11). Other reported events occurred at a rate of less than 0.10 events per patient per year.

Events reported to have occurred within several hours of administration of EPOGEN® were rare, mild, and transient, and included injection site stinging in dialysis patients and flu-like symptoms such as arthralgias and myalgias.

In all studies analyzed to date, EPOGEN® administration was generally well-tolerated, irrespective of the route of administration.

Hypertension: Increases in blood pressure have been reported in clinical trials, often during the first 90 days of therapy. On occasion, hypertensive encephalopathy and seizures have been observed in patients with CRF treated with EPOGEN®. When data from all patients in the US Phase 3 multicenter trial were analyzed, there was an apparent trend of more reports of hypertensive adverse events in patients on dialysis with a faster rate of rise of hematocrit (greater than 4 hematocrit points in any 2-week period). However, in a double-blind, placebo-controlled trial, hypertensive adverse events were not reported at an increased rate in the group treated with EPOGEN® (150 Units/kg TIW) relative to the placebo group.

Seizures: There have been 47 seizures in 1010 patients on dialysis treated with EPOGEN® in clinical trials, with an exposure of 986 patient-years for a rate of approximately 0.048 events per patient-year. However, there appeared to be a higher rate of seizures during the first 90 days of therapy (occurring in approximately 2.5% of patients) when compared to subsequent 90-day periods. The baseline incidence of seizures in the untreated dialysis population is difficult to determine; it appears to be in the range of 5% to 10% per patient-year.[26-28]

Thrombotic Events: In clinical trials where the maintenance hematocrit was 35 ± 3% on EPOGEN®, clotting of the vascular access (A-V shunt) has occurred at an annualized rate of about 0.25 events per patient-year, and other thrombotic events (eg, myocardial infarction, cerebral vascular accident, transient ischemic attack, and pulmonary embolism) occurred at a rate of 0.04 events per patient-year. In a separate study of 1111 untreated dialysis patients, clotting of the vascular access occurred at a rate of 0.50 events per patient-year. However, in CRF patients on hemodialysis who also had clinically evident ischemic heart disease or congestive heart failure, the risk of A-V shunt thrombosis was higher (39% vs 29%, $p < 0.001$), and myocardial infarctions, vascular ischemic events, and venous thrombosis were increased, in patients targeted to a hematocrit of 42 ± 3% compared to those maintained at 30 ± 3% (see WARNINGS).

In patients treated with commercial EPOGEN®, there have been rare reports of serious or unusual thrombo-embolic events including migratory thrombophlebitis, microvascular thrombosis, pulmonary embolus, and thrombosis of the retinal artery, and temporal and renal veins. A causal relationship has not been established.

Allergic Reactions: There have been no reports of serious allergic reactions or anaphylaxis associated with EPOGEN® administration during clinical trials. Skin rashes and urticaria have been observed rarely and when reported have generally been mild and transient in nature.

There have been rare reports of potentially serious allergic reactions including urticaria with associated respiratory symptoms or circumoral edema, or urticaria alone. Most reactions occurred in situations where a causal relationship could not be established. Symptoms recurred with rechallenge in a few instances, suggesting that allergic reactivity may occasionally be associated with EPOGEN® therapy.

There has been no evidence for development of antibodies to erythropoietin in patients tested to date, including those receiving EPOGEN® for over 4 years. Nevertheless, if an anaphylactoid reaction occurs, EPOGEN® should be immediately discontinued and appropriate therapy initiated.

Zidovudine-treated HIV-infected Patients

Adverse events reported in clinical trials with EPOGEN® in zidovudine-treated HIV-infected patients were consistent with the progression of HIV infection. In double-blind, placebo-controlled studies of three-months duration involving approximately 300 zidovudine-treated HIV-infected patients, adverse events with an incidence of ≥ 10% in either patients treated with EPOGEN® or placebo-treated patients were:

PERCENT OF PATIENTS REPORTING EVENT

Event	Patients Treated with EPOGEN® (n = 144)	Placebo-Treated Patients (n = 153)
Pyrexia	38%	29%
Fatigue	25%	31%
Headache	19%	14%
Cough	18%	14%
Diarrhea	16%	18%
Rash	16%	8%
Congestion, Respiratory	15%	10%
Nausea	15%	12%
Shortness of Breath	14%	13%
Asthenia	11%	14%
Skin Reaction, Medication Site	10%	7%
Dizziness	9%	10%

There were no statistically significant differences between treatment groups in the incidence of the above events.

In the 297 patients studied, EPOGEN® was not associated with significant increses in opportunistic infections or mortality.[22] In 71 patients from this group treated with EPOGEN® at 150 Units/kg TIW, serum p24 antigen levels did not appear to increase.[23] Preliminary data showed no enhancement of HIV replication in infected cell lines in vitro.[22]

Peripheral white blood cell and platelet counts are unchanged following EPOGEN® therapy.

Allergic Reactions: Two zidovudine-treated HIV-infected patients had urticarial reactions within 48 hours of their first exposure to study medication. One patient was treated with EPOGEN® and one was treated with placebo (EPOGEN® vehicle alone). Both patients had positive immediate skin tests against their study medication with a negative saline control. The basis for this apparent pre-existing hypersensitivity to components of the EPOGEN® formulation is unknown but may be related to HIV-induced immunosuppression or prior exposure to blood products.

Seizures: In double-blind and open-label trials of EPOGEN® in zidovudine-treated HIV-infected patients, 10 patients have experienced seizures.[22] In general, these seizures appear to be related to underlying pathology, such as meningitis or cerebral neoplasms, not EPOGEN® therapy.

Cancer Patients on Chemotherapy

Adverse experiences reported in clinical trials with EPOGEN® in cancer patients were consistent with the underlying disease state. In double-blind, placebo-controlled studies of up to 3 months duration involving 131 cancer patients, adverse effects with an incidence > 10% in either patients treated with EPOGEN® or placebo-treated patients were as indicated below:

PERCENT OF PATIENTS REPORTING EVENT

Event	Patients Treated with EPOGEN® (n = 63)	Placebo-Treated Patients (n = 68)
Pyrexia	29%	19%
Diarrhea	21%[a]	7%
Nausea	17%[b]	32%
Vomiting	17%	15%
Edema	17%[c]	1%
Asthenia	13%	16%
Fatigue	13%	15%
Shortness of Breath	13%	9%
Paresthesia	11%	6%
Upper Respiratory Infection	11%	4%
Dizziness	5%	12%
Trunk Pain	3%[d]	16%

[a] $p = 0.041$,
[b] $p = 0.069$,
[c] $p = 0.016$,
[d] $p = 0.017$

Although some statistically significant differences between patients being treated with EPOGEN® and placebo-treated patients were noted, the overall safety profile of EPOGEN® appeared to be consistent with the disease process of advanced cancer. During double-blind and subsequent open-label therapy in which patients (n = 72 for total exposure to EPOGEN®) were treated for up to 32 weeks with doses as high as 927 Units/kg, the adverse experience profile of EPOGEN® was consistent with the progression of advanced cancer.

Based on comparable survival data and on the percentage of patients treated with EPOGEN® and placebo-treated patients who discontinued therapy due to death, disease progression, or adverse experiences (22% and 13%, respectively, $p = 0.25$), the clinical outcome in patients treated with EPOGEN® and placebo-treated patients appeared to be similar. Available data from animal tumor models and measurement of proliferation of solid tumor cells from clinical biopsy specimens in response to EPOGEN® suggest that EPOGEN® does not potentiate tumor growth. Nevertheless, as a growth factor, the possibility that EPOGEN® may potentiate growth of some tumors, particularly myeloid tumors, cannot be excluded. A randomized controlled Phase 4 study is currently ongoing to further evaluate this issue. The mean peripheral white blood cell count was unchanged following EPOGEN® therapy compared to the corresponding value in the placebo-treated group.

Surgery Patients

Adverse events with an incidence of ≥ 10% are shown in the following table:

PERCENT OF PATIENTS REPORTING EVENT

Event	Patients Treated with EPOGEN® 300 U/kg (n = 112)[a]	Patients Treated with EPOGEN® 100 U/kg (n = 101)[a]	Placebo-treated Patients (n = 103)[a]	Patients Treated with EPOGEN® 600 U/kg (n = 73)[b]	Patients Treated with EPOGEN® 300 Y/kg (n = 72)[b]
Pyrexia	51%	50%	60%	47%	42%
Nausea	48%	43%	45%	45%	58%
Constipation	43%	42%	43%	51%	53%
Skin reaction, Medication site	25%	19%	22%	26%	29%
Vomiting	22%	12%	14%	21%	29%
Skin Pain	18%	18%	17%	5%	4%
Pruritus	16%	16%	14%	14%	22%
Insomnia	13%	16%	13%	21%	18%
Headache	13%	11%	9%	10%	19%
Dizziness	12%	9%	12%	11%	21%
Urinary Tract Infection	12%	3%	11%	11%	8%
Hypertension	10%	11%	10%	5%	10%
Diarrhea	10%	7%	12%	10%	6%
Deep Venous Thrombosis	10%	3%	5%	0%[c]	0%[c]
Dyspepsia	9%	11%	6%	7%	8%
Anxiety	7%	2%	11%	11%	4%
Edema	6%	11%	8%	11%	7%

[a] Study including patients undergoing orthopedic surgery treated with EPOGEN® or placebo for 15 days
[b] Study including patients undergoing orthopedic surgery treated with EPOGEN® 600 Units/kg weekly × 4 or 300 Units/kg daily × 15

Thrombotic/Vascular Events: In three double-blind, placebo-controlled orthopedic surgery studies, the rate of deep venous thrombosis (DVT) was similar among Epoetin alfa and placebo-treated patients in the recommended population of patients with a pretreatment hemoglobin of > 10 to ≤ 13 g/dL.[14,16,24] However, in 2 of 3 orthopedic surgery studies the overall rate (all pretreatment hemoglobin groups combined) of DVTs detected by postoperative ultrasonography and/or surveillance venography was higher in the group treated with Epoetin alfa than in the placebo-treated group (11% vs 6%). This finding was attributable to the difference in DVT rates observed in the subgroup of patients with pretreatment hemoglobin > 13 g/dL. However, the incidence of DVTs was within the range of that reported in the literature for orthopedic surgery patients.

In the orthopedic surgery study of patients with pretreatment hemoglobin of > 10 to ≤ 13 g/dL which compared two dosing regimens (600 Units/kg weekly × 4 and 300 Units/kg daily × 15), 4 subjects in the 600 Units/kg weekly EPOGEN® group (5%) and no subjects in the 300 Units/kg daily group had a thrombotic vascular event during the study period.[15]

In a study examining the use of Epoetin alfa in 182 patients scheduled for coronary artery bypass graft surgery 23% of patients treated with Epoetin alfa and 29% treated with placebo experienced thrombotic/vascular events. There were 4 deaths among the Epoetin alfa-treated patients that were

associated with a thrombotic/vascular event. A causative role of Epoetin alfa cannot be excluded (see WARNINGS).

OVERDOSAGE

The maximum amount of EPOGEN® that can be safely administered in single or multiple doses has not been determined. Doses of up to 1500 Units/kg TIW for 3 to 4 weeks have been administered without any direct toxic effects of EPOGEN® itself.[6] Therapy with EPOGEN® can result in polycythemia if the hematocrit is not carefully monitored and the dose appropriately adjusted. If the suggested target range is exceeded, EPOGEN® may be temporarily withheld until the hematocrit returns to the suggested target range; EPOGEN® therapy may then be resumed using a lower dose (see DOSAGE AND ADMINISTRATION). If polycythemia is of concern, phlebotomy may be indicated to decrease the hematocrit.

DOSAGE AND ADMINISTRATION

Chronic Renal Failure Patients

Starting doses of EPOGEN® over the range of 50 to 100 Units/kg TIW have been shown to be safe and effective in increasing hematocrit and eliminating transfusion dependency in patients with CRF (see CLINICAL EXPERIENCE). The dose of EPOGEN® should be reduced as the hematocrit approaches 36% or increases by more than 4 points in any 2-week period. The dosage of EPOGEN® must be individualized to maintain the hematocrit within the suggested target range. At the physician's discretion, the suggested target hematocrit range may be expanded to achieve maximal patient benefit.

EPOGEN® may be given either as an IV or SC injection. In patients on hemodialysis, EPOGEN® usually has been administered as an IV bolus TIW. While the administration of EPOGEN® is independent of the dialysis procedure, EPOGEN® may be administered into the venous line at the end of the dialysis procedure to obviate the need for additional venous access. In patients with CRF not on dialysis, EPOGEN® may be given either as an IV or SC injection.

Patients who have been judged competent by their physicians to self-administer EPOGEN® without medical or other supervision may give themselves either an IV or SC injection. The table below provides general therapeutic guidelines for patients with CRF:

Starting Dose:	50 to 100 Units/kg TIW; IV or SC
Reduce Dose When:	1. Hct. approaches 36% or, 2. Hct. increases > 4 points in any 2-week period
Increase Dose If:	Hct. does not increase by 5 to 6 points after 8 weeks of therapy, and hct. is below suggested target range
Maintenance Dose:	Individually titrate
Suggested Target Hct. Range:	30% to 36%

During therapy, hematological parameters should be monitored regularly (see LABORATORY MONITORING).

Pre-therapy Iron Evaluation: Prior to and during EPOGEN® therapy, the patient's iron stores, including transferrin saturation (serum iron divided by iron-binding capacity) and serum ferritin, should be evaluated. Transferrin saturation should be at least 20%, and ferritin should be at least 100 ng/mL. Virtually all patients will eventually require supplemental iron to increase or maintain transferrin saturation to levels that will adequately support erythropoiesis stimulated by EPOGEN®.

Dose Adjustment: Following EPOGEN® therapy, a period of time is required for erythroid progenitors to mature and be released into circulation resulting in an eventual increase in hematocrit. Additionally, red blood cell survival time affects hematocrit and may vary due to uremia. As a result, the time required to elicit a clinically significant change in hematocrit (increase or decrease) following any dose adjustment may be 2 to 6 weeks.

Dose adjustment should not be made more frequently than once a month, unless clinically indicated. After any dose adjustment, the hematocrit should be determined twice weekly for at least 2 to 6 weeks (see LABORATORY MONITORING).

- If the hematocrit is increasing and approaching 36%, the dose should be reduced to maintain the suggested target hematocrit range. If the reduced dose does not stop the rise in hematocrit, and it exceeds 36%, doses should be temporarily withheld until the hematocrit begins to decrease, at which point therapy should be reinitiated at a lower dose.
- At any time, if the hematocrit increases by more than 4 points in a 2-week period, the dose should be immediately decreased. After the dose reduction, the hematocrit should be monitored twice weekly for 2 to 6 weeks, and further dose adjustments should be made as outlined in MAINTENANCE DOSE.
- If a hematocrit increase of 5 to 6 points is not achieved after an 8-week period and iron stores are adequate (see DELAYED OR DIMINISHED RESPONSE), the dose of EPOGEN® may be incrementally increased. Further increases may be made at 4 to 6 week intervals until the desired response is attained.

Maintenance Dose: The maintenance dose must be individualized for each patient on dialysis. In the US Phase 3 multicenter trial in patients on hemodialysis, the median maintenance dose was 75 Units/kg TIW, with a range from 12.5 to 525 Units/kg TIW. Almost 10% of the patients required a dose of 25 Units/kg or less, and approximately 10% of the patients required more than 200 Units/kg TIW to maintain their hematocrit in the suggested target range.

If the hematocrit remains below or falls below the suggested target range, iron stores should be re-evaluated. If the transferrin saturation is less than 20%, supplemental iron should be administered. If the transferrin saturation is greater than 20%, the dose of EPOGEN® may be increased. Such dose increases should not be made more frequently than once a month, unless clinically indicated, as the response time of the hematocrit to a dose increase can be 2 to 6 weeks. Hematocrit should be measured twice weekly for 2 to 6 weeks following dose increases. In patients with CRF not on dialysis, the maintenance dose must also be individualized. EPOGEN® doses of 75 to 150 Units/kg per week have been shown to maintain hematocrits of 36% to 38% for up to 6 months.

Delayed or Diminished Response: Over 95% of patients with CRF responded with clinically significant increases in hematocrit, and virtually all patients were transfusion-independent within approximately 2 months of initiation of EPOGEN® therapy.

If a patient fails to respond or maintain a response, other etiologies should be considered and evaluated as clinically indicated (see PRECAUTIONS for discussion of delayed or diminished response).

Zidovudine-treated HIV-Infected Patients

Prior to beginning EPOGEN®, it is recommended that the endogenous serum erythropoietin level be determined (prior to transfusion). Available evidence suggests that patients receiving zidovudine with endogenous serum erythropoietin levels > 500 mUnits/mL are unlikely to respond to therapy with EPOGEN®.

Starting Dose: For patients with serum erythropoietin levels ≤ 500 mUnits/mL who are receiving a dose of zidovudine ≤ 4200 mg/week, the recommended starting dose of EPOGEN® is 100 Units/kg as an IV or SC injection TIW for 8 weeks.

Increase Dose: During the dose adjustment phase of therapy, the hematocrit should be monitored weekly. If the response is not satisfactory in terms of reducing transfusion requirements or increasing hematocrit after 8 weeks of therapy, the dose of EPOGEN® can be increased by 50 to 100 Units/kg TIW. Response should be evaluated every 4 to 8 weeks thereafter and the dose adjusted accordingly by 50 to 100 Units/kg increments TIW. If patients have not responded satisfactorily to an EPOGEN® dose of 300 Units/kg TIW, it is unlikely that they will respond to higher doses of EPOGEN®.

Maintenance Dose: After attainment of the desired response (ie, reduced transfusion requirements or increased hematocrit), the dose of EPOGEN® should be titrated to maintain the response based on factors such as variations in zidovudine dose and the presence of intercurrent infectious or inflammatory episodes. If the hematocrit exceeds 40%, the dose should be discontinued until the hematocrit drops to 36%. The dose should be reduced by 25% when treatment is resumed and then titrated to maintain the desired hematocrit.

Cancer Patients on Chemotherapy

Baseline endogenous serum erythropoietin levels varied among patients in these trials with approximately 75% (n = 83/110) having endogenous serum erythropoietin levels < 132 mUnits/mL, and approximately 4% (n = 4/110) of patients having endogenous serum erythropoietin levels > 500 mUnits/mL. In general, patients with lower baseline serum erythropoietin levels responded more vigorously to EPOGEN® than patients with higher erythropoietin levels. Although no specific serum erythropoietin level can be stipulated above which patients would be unlikely to respond to EPOGEN® therapy, treatment of patients with grossly elevated serum erythropoietin levels (eg, > 200 mUnits/mL) is not recommended. The hematocrit should be monitored on a weekly basis in patients receiving EPOGEN® therapy until hematocrit becomes stable.

Starting Dose: The recommended starting dose of EPOGEN® is 150 Units/ kg SC TIW.

Dose Adjustment: If the response is not satisfactory in terms of reducing transfusion requirements or increasing hematocrit after 8 weeks of therapy, the dose of EPOGEN® can be increased up to 300 Units/kg TIW. If patients have not responded satisfactorily to an EPOGEN® dose of 300 Units/kg TIW, it is unlikely that they will respond to higher doses of EPOGEN®. If the hematocrit exceeds 40%, the dose of EPOGEN® should be withheld until the hematocrit falls to 36%. The dose of EPOGEN® should be reduced by 25% when treatment is resumed and titrated to maintain the desired hematocrit. If the initial dose of EPOGEN® includes a very rapid hematocrit response (eg, an increase of more than 4 percentage points in any 2-week period), the dose of EPOGEN® should be reduced.

Surgery Patients

Prior to initiating treatment with EPOGEN® a hemoglobin should be obtained to establish that it is > 10 to ≤ 13 g/dL.[14] The recommended dose of EPOGEN® is 300 Units/kg/day subcutaneously for 10 days before surgery, on the day of surgery, and for 4 days after surgery.

An alternate dose schedule is 600 Units/kg EPOGEN® subcutaneously in once weekly doses (21, 14, and 7 days before surgery) plus a fourth dose on the day of surgery.[15]

All patients should receive adequate iron supplementation. Iron supplementation should be initiated no later than the beginning of treatment with EPOGEN® and should continue throughout the course of therapy.

PREPARATION AND ADMINISTRATION OF EPOGEN®

1. Do not shake. It is not necessary to shake EPOGEN®. Prolonged vigorous shaking may denature any glycoprotein, rendering it biologically inactive.
2. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use any vials exhibiting particulate matter or discoloration.
3. Using aseptic techniques, attach a sterile needle to a sterile syringe. Remove the flip top from the vial containing EPOGEN®, and wipe the septum with a disinfectant. Insert the needle into the vial, and withdraw into the syringe an appropriate volume of solution.
4. Single-dose 1 mL vial contains no preservative. Use one dose per vial; do not re-enter the vial. Discard unused portions.
   Multidose 1 mL and 2 mL vials contain preservative. Store at 2° to 8°C after initial entry and between doses. Discard 21 days after initial entry.
5. Do not dilute or administer in conjunction with other drug solutions. However, at the time of SC administration, preservative-free EPOGEN® from single-use vials may be admixed in a syringe with bacteriostatic 0.9% sodium chloride injection, USP, with benzyl alcohol 0.9% (bacteriostatic saline) at a 1:1 ratio using aseptic technique. The benzyl alcohol in the bacteriostatic saline acts as a local anesthetic which may ameliorate SC injection site discomfort. Admixing is not necessary when using the multidose vials of EPOGEN® containing benzyl alcohol.

HOW SUPPLIED

EPOGEN®, containing Epoetin alfa, is available in the following packages:

1 mL **Single-dose, Preservative-free** Solution
- 2000 Units/mL (NDC 55513-126-10)
- 3000 Units/mL (NDC 55513-267-10)
- 4000 Units/mL (NDC 55513-148-10)
- 10,000 Units/mL (NDC 55513-144-10)

Supplied in cartons containing 10 single-dose vials.

2 mL **Multidose, Preserved** Solution
- 10,000 Units/mL (NDC 55513-283-10)

1 mL **Multidose, Preserved** Solution
- 20,000 Units/mL (NDC 55513-478-10)

Supplied in cartons containing 10 multidose vials.

STORAGE

Store at 2° to 8°C (36° to 46°F). Do not freeze or shake.

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Epogen—Cont.

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AMGEN®
Manufactured by:
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Thousand Oaks, CA
91320-1789
Issue Date: 12/23/96

EPOGEN®(Epoetin alfa)
Information for Home Dialysis Patients

AMGEN®
EPOGEN®
(RECOMBINANT EPOETIN ALFA)

What is EPOGEN® and how does it work?

EPOGEN® is a copy of human erythropoietin, a hormone produced primarily by healthy kidneys. EPOGEN® replaces the erythropoietin that the failed kidneys can no longer produce, and signals the bone marrow to make the oxygen-carrying red blood cells once again. EPOGEN® is produced in mammalian cells that have been genetically altered by the addition of gene for the natural substance erythropoietin.

How should I take EPOGEN®?

In those situations where your doctor has determined that you, as a home dialysis patient, can self-administer EPOGEN®, you will receive instruction on how much EPOGEN® to use, how to inject it, how often you should inject it, and how you should dispose of the unused portions of each vial.

You will be instructed to monitor your blood pressure carefully everyday and to report any changes outside of the guidelines that your doctor has given you. When the number of red blood cells increases, your blood pressure can also increase, so your doctor may prescribe some new or additional blood pressure medication. Be sure to follow your doctor's orders. You may also be instructed to have certain laboratory tests, such as additional hematocrit or iron level measurements, done more frequently. You may be asked to report these tests to your doctor or dialysis center. Also, your doctor may prescribe additional iron for you to take. Be sure to comply with your doctor's orders.

Continue to check your access, as your doctor or nurse has shown you, to make sure it is working. Be sure to let your health care professional know right away if there is a problem.

Allergy to EPOGEN®

Patients occasionally experience redness, swelling, or itching at the site of injection of EPOGEN®. This may indicate an allergy to the components of EPOGEN®, or it may indicate a local reaction. If you have a local reaction, consult your doctor. A potentially more serious reaction would be a generalized allergy to EPOGEN®, which could cause a rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases of generalized allergy may be life-threatening. If you think you are having a generalized allergic reaction, stop taking EPOGEN® and notify a doctor or emergency medical personnel imediately.

How will I know if EPOGEN® is working?

The effectiveness of EPOGEN® is measured by the increase in hematocrit (the amount of red blood cells in the blood) that results from EPOGEN® therapy. The rise in hematocrit is not immediate. It usually takes about 2 to 6 weeks before the hematocrit starts to rise. The amount of time it takes, and the dose of EPOGEN® that is needed to make the hematocrit increase, varies from patient to patient.

What is the most important information I should know about EPOGEN® and CHRONIC RENAL FAILURE?

EPOGEN® has been prescribed for you by your doctor because you:

1. Have anemia due to your kidney disease.
2. Are able to dialyze at home.
3. Have been determined to be able to administer EPOGEN® without direct medical or other supervision.

A lack of energy or feeling of tiredness is the major symptom of anemia. Additional symptoms include shortness of breath, chest pain, and feeling cold all the time. The reason for these symptoms is that there is a lack of red blood cells. Red blood cells carry oxygen, which is important for all of the body's functions. When there are fewer red blood cells, the body does not get all the oxygen it needs.

Kidneys remove toxins from the blood; they also measure the amount of oxygen in the blood. If there is not enough oxygen, the kidneys will produce a hormone called erythropoietin. Erythropoietin is released into the bloodstream and travels to the bone marrow where red blood cells are made. Erythropoietin signals the bone marrow to make more oxygen-carrying red blood cells.

As the kidneys fail, they stop cleansing toxins from your body. They also make less erythropoietin than they should. Therefore, the bone marrow does not receive a strong-enough signal to make the oxygen-carrying red blood cells. Fewer red blood cells are produced so the muscles, brain, and other parts of the body do not get the oxygen they need to function properly.

Most patients treated with EPOGEN® no longer need blood transfusions. However, certain medical conditions, or unexpected blood loss, may result in the need for a transfusion.

What do I need to know if I am giving myself EPOGEN® injections?

When you receive your EPOGEN® from the dialysis center, doctor's office or home dialysis supplier, always check to see that:

1. The name EPOGEN® appears on the carton and vial label.
2. You will be able to use EPOGEN® before the expiration date stamped on the package.

The EPOGEN® solution in the vial should always be clear and colorless. Do not use EPOGEN® if the contents of the vial appear discolored or cloudy, or if the vial appears to contain lumps, flakes, or particles. In addition, if the vial has been shaken vigorously, the solution may appear to be frothy and should not be used. Therefore, care should be taken not to shake the EPOGEN® vial vigorously before use.

Single Use Vials–S

If you have been prescribed EPOGEN® vials for single use, your vial will have a capital "S" with a number next to it identifying the concentration of EPOGEN® in the vial, printed in a colored dot on the front left side of the label (for example, "S2" identifies a single use vial with 2000 Units/mL). Single use means the vial cannot be used more than once, and any unused portion of the vial should be discarded as directed by your doctor or dialysis center.

Multidose Use Vials–M

If you have been prescribed EPOGEN® Multidose vials, your vial will have a capital "M" with a number under it identifying the concentration of EPOGEN® in the vial, printed in a colored dot on the front left side of the label (for example, "M10" identifies a Multidose vial with 10,000 Units/mL). Multidose EPOGEN® can be used to inject multiple doses as prescribed by your doctor, and may be stored in the refrigerator (but not the freezing compartment) between doses for up to 21 days. Follow your doctor's or dialysis center's instructions on what to do with the used vials.

How should I store EPOGEN®?

EPOGEN® should be stored in the refrigerator, but not in the freezing compartment. Do not let the vial freeze and do not leave it in direct sunlight. Do not use a vial of EPOGEN® that has been frozen or after the expiration date that is stamped on the label. If you have any questions about the safety of a vial of EPOGEN® that has been subjected to temperature extremes, be sure to check with your dialysis unit staff.

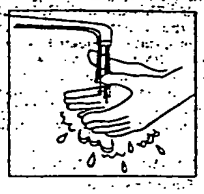
Always use the correct syringe

Your doctor has instructed you on how to give yourself the correct dosage of EPOGEN®. This dosage will usually be measured in Units per milliliter or CCs. It is important to use a syringe that is marked in tenths of milliliters (for example, 0.2 mL or CC). Failure to use the proper syringe can lead to a mistake in dosage, and you may receive too much or too little EPOGEN®. Too little EPOGEN® may not be effective in increasing your hematocrit, and too much EPOGEN® may lead to a hematocrit that is too high. Only use disposable syringes and needles as they do not require sterilization; they should be used once and disposed of as instructed by your doctor.

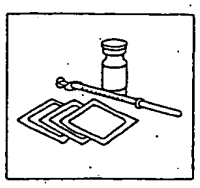
IMPORTANT: TO HELP AVOID CONTAMINATION AND POSSIBLE INFECTION, FOLLOW THESE INSTRUCTIONS EXACTLY.

PREPARING THE DOSE

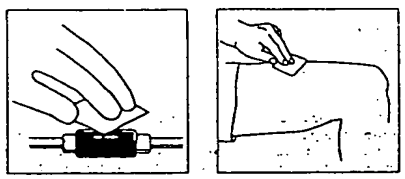
1. Wash your hands thoroughly with soap and water before preparing the medication.



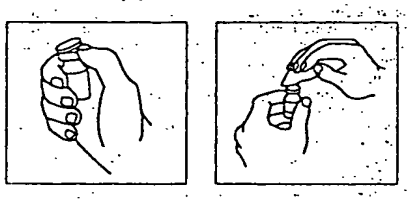
2. Check the date on the EPOGEN® vial to be sure that the drug has not expired.
3. Remove the vial of EPOGEN® from the refrigerator and allow it to reach room temperature. Unless you are using a Multidose vial, each EPOGEN® vial is designed to be used only once. It is not necessary to shake EPOGEN®. Prolonged vigorous shaking may damage the product. Assemble the other supplies you will need for your injection.



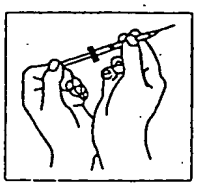
4. Hemodialysis patients should wipe off the venous port of the hemodialysis tubing with an antiseptic swab. Peritoneal dialysis patients should cleanse the skin with an antiseptic swab where the injection is to be made.



5. Flip off the red protective cap but do not remove the gray rubber stopper. Wipe the top of the gray rubber stopper with an antiseptic swab.

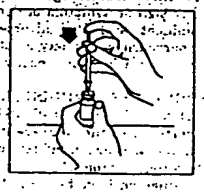


6. Using a syringe and needle designed for subcutaneous injection, draw air into the syringe by pulling back on the plunger. The amount of air should be equal to your EPOGEN® dose.

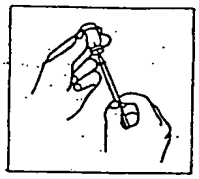


7. Carefully remove the needle cover. Put the needle through the gray rubber stopper of the EPOGEN® vial.

8. Push the plunger in to discharge air into the vial. The air injected into the vial will allow EPOGEN® to be easily withdrawn into the syringe.



9. Turn the vial and syringe upside down in one hand. Be sure the tip of the needle is in the EPOGEN® solution. Your other hand will be free to move the plunger. Draw back on the plunger slowly to draw the correct dose of EPOGEN® into the syringe.

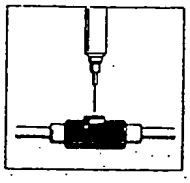


10. Check for air bubbles. The air is harmless, but too large an air bubble will reduce the EPOGEN® dose. To remove air bubbles, gently tap the syringe to move the air bubbles to the top of the syringe, then use the plunger to push the solution and the air back into the vial. Then remeasure your correct dose of EPOGEN®.
11. Double check your dose. Remove the needle from the vial. Do not lay the syringe down or allow the needle to touch anything.

INJECTING THE DOSE

Patients on home hemodialysis using the intravenous injection route:

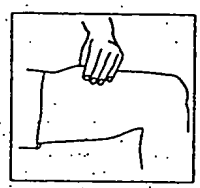
1. Insert the needle of the syringe into the previously cleansed venous port and inject the EPOGEN®.



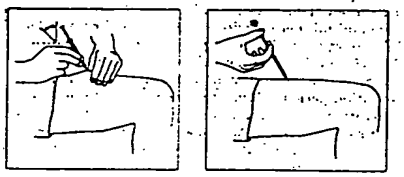
2. Remove the syringe and dispose of the whole unit. ***Use the disposable syringe only once.*** Dispose of syringes and needles as directed by your doctor, by following these simple steps:
   - Place all used needles and syringes in a hard plastic container with a screw-on-cap, or a metal container with a plastic lid, such as a coffee can properly labeled as to content. If a metal container is used, cut a small hole in the plastic lid and tape the lid to the metal container. If a hard-plastic container is used, always screw the cap on tightly after each use. When the container is full, tape around the cap or lid, and dispose of according to your doctor's instructions.
   - Do not use glass or clear plastic containers, or any container that will be recycled or returned to a store.
   - Always store the container out of the reach of children.
   - Please check with your doctor, nurse, or pharmacist for other suggestions. There may be special state and local laws that they will discuss with you.

Patients on home peritoneal dialysis or home hemodialysis using the subcutaneous route:

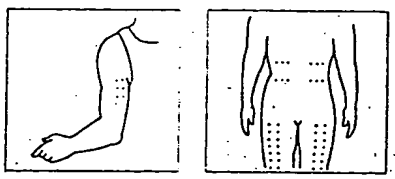
1. With one hand, stabilize the previously cleansed skin by spreading it or by pinching up a large area with your free hand.



2. Hold the syringe with the other hand, as you would a pencil. Double check that the correct amount of EPOGEN® is in the syringe. Insert the needle straight into the skin (90 degree angle). Pull the plunger back slightly. If blood comes into the syringe, do not inject EPOGEN®, as the needle has entered a blood vessel; withdraw the syringe and inject at a different site. Inject the EPOGEN® by pushing the plunger all the way down.



3. Hold an antiseptic swab near the needle and pull the needle straight out of the skin. Press the antiseptic swab over the injection site for several seconds.
4. ***Use the disposable syringe only once.*** Dispose of syringes and needles as directed by your doctor, by following these simple steps:
   - Place all used needles and syringes in a hard plastic container with a screw-on-cap, or a metal container with a plastic lid, such as a coffee can properly labeled as to content. If a metal container is used, cut a small hole in the plastic lid and tape the lid to the metal container. If a hard-plastic container is used, always screw the cap on tightly after each use. When the container is full, taper around the cap or lid, and dispose of according to your doctor's instructions.
   - Do not use glass or clear plastic containers, or any container that will be recycled or returned to a store.
   - Always store the container out of the reach of children.
   - Please check with your doctor, nurse, or pharmacist for other suggestions. There may be special state and local laws that they will discuss with you.
5. Always change the site for each injection as directed. Occasionally a problem may develop at the injection site. If you notice a lump, swelling, or bruising that doesn't go away, contact your doctor. You may wish to record the site just used so that you can keep track.



USAGE IN PREGNANCY

If you are pregnant or nursing a baby, consult your doctor before using EPOGEN®.

IMPORTANT NOTES

Since you are a home dialysis patient and your doctor allows you to self-administer EPOGEN®, please note the following:

1. Always follow the instructions of your doctor concerning the dosage and administration of EPOGEN®. Do not change the dose or instructions for administration of EPOGEN® without consulting your doctor.
2. Your doctor will tell you what to do if you miss a dose of EPOGEN®. Always keep a spare syringe and needle on hand.
3. Always consult your doctor if you notice anything unusual about your condition or your use of EPOGEN®.

AMGEN®
Manufactured by:
Amgen Inc.
1840 DeHavilland Drive
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91320-1789

Issue Date: 11/14/96 US EPO PI Copy Rev

P30035D 25M/1-97
Shown in Product Identification Guide, page 304

INFERGEN®
(Interferon alfacon-1)

DESCRIPTION

Interferon alfacon-1 is a recombinant non-naturally occurring type-I interferon. The 166-amino acid sequence of Interferon alfacon-1 was derived by scanning the sequences of several natural interferon alpha subtypes and assigning the most frequently observed amino acid in each corresponding position.[1] Four additional amino acid changes were made to facilitate the molecular construction, and a corresponding synthetic DNA sequence was constructed using [illegible] synthesis methodology. Interferon alfacon-1 differs from interferon alfa-2 at 20/166 amino acids (88% homologous). In comparison with interferon beta shows identity at [illegible] of the amino acid positions. Interferon alfacon-1 is produced in *Escherichia coli (E coli)* cells that have been genetically altered by insertion of a synthetically constructed sequence that codes for Interferon alfacon-1. Prior to final purification, Interferon alfacon-1 is allowed to oxidize to its native state, and its final purity is achieved by sequential passage over a series of chromatography columns. This protein has a molecular weight of 19,434 daltons. Infergen® is the Amgen Inc. trademark for Interferon alfacon-1.

Infergen is a sterile, clear, colorless, preservative-free liquid formulated with 100 mM sodium chloride and 25 mM sodium phosphate at pH 7.0 ± 0.2. The product is available in single-use vials and prefilled syringes containing 9 mcg and 15 mcg Interferon alfacon-1 at a fill volume of 0.3 mL and 0.5 mL, respectively. Infergen vials and prefilled syringes contain 0.03 mg/mL of Interferon alfacon-1, 5.9 mg/mL sodium chloride, and 3.8 mg/mL sodium phosphate in Water for Injection, USP. The Infergen SingleJect™ prefilled syringe has a glass barrel and a 26 gauge, 5/8 inch needle. Infergen is to be administered undiluted by subcutaneous (SC) injection.

Formulation, filling, and packaging operations for Infergen are performed by Amgen Puerto Rico, a wholly-owned subsidiary of Amgen Inc.

CLINICAL PHARMACOLOGY

General

Interferons are a family of naturally occurring small protein molecules with molecular weights of 15,000 to 21,000 daltons that are produced and secreted by cells in response to viral infections or to various synthetic and biological inducers. Two major classes of interferons have been identified (ie, type-I and type-II). Type-I interferons include a family of more than 25 interferon alphas as well as interferon beta and interferon omega. While all alpha interferons have similar biological effects, not all the activities are shared by each alpha interferon and, in many cases, the extent of activity varies substantially for each interferon subtype.

All type-I interferons share common biological activities generated by binding of interferon to the cell-surface receptor, leading to the production of several interferon-stimulated gene products. Type-I interferons induce pleiotropic biologic responses which include antiviral, antiproliferative and immunomodulatory effects, regulation of cell surface major histocompatibility antigen (HLA class I and class II) expression and regulation of cytokine expression. Examples of interferon-stimulated gene products include 2'5' oligoadenylate synthetase (2'5' OAS) and β-2 microglobulin.

The antiviral, antiproliferative, NK cell activation, and gene-induction activities of Infergen have been compared with other recombinant alfa interferons in *in vitro* assays and have demonstrated similar ranges of activity. Infergen exhibited at least five times higher specific activity in more than Interferon alfa-2a and Interferon alfa-2b.[2] Comparison of Infergen with a WHO international potency standard for recombinant interferon alfa (83/514) revealed that the specific activity of Infergen in both an *in vitro* antiviral cytopathic effect assay and an antiproliferative assay was $> 10^9$ U/mg. However, correlation between *in vitro* activity and clinical activity of any interferon is unknown.

Pharmacokinetics and Pharmacodynamics

The pharmacokinetic properties of Infergen have not been evaluated in patients with chronic hepatitis C. Pharmacokinetic profiles were evaluated in normal, healthy volunteer subjects after SC injection of 1, 3, or 9 mcg Interferon alfacon-1. Plasma levels of Infergen after SC administration of any dose were too low to be detected by either ELISA or by inhibition of viral cytopathic effect. However, analysis of Infergen-induced cellular products (induction of 2'5' OAS and β-2 microglobulin) after treatment in these subjects revealed a statistically significant, dose-related increase in the area under the curve (AUC) for the levels of 2'5' OAS or β-2 microglobulin induced over time ($p < 0.001$ for all comparisons). Concentrations of 2'5' OAS were maximal in 24 hours after dosing, while serum levels of β-2 microglobulin appeared to reach a maximum 24 to 36 hours after dosing. The dose-response relationships observed for 2'5' OAS and β-2 microglobulin were indicative of biological activity after SC administration of 1 to 9 mcg Infergen.

Preclinical Experience

All interferons have been shown to be highly species specific. Antiviral activity of Infergen was observed in the rhesus monkey LLC cell line and golden Syrian hamster BHK cell line. Antiviral activity of Infergen in the golden Syrian hamster was confirmed further *in vivo*.[3] Pharmacokinetic studies of Infergen in golden Syrian hamsters and rhesus monkeys demonstrated rapid absorption following SC in-

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5. Administer ORTHOCLONE OKT3 as a single intravenous (bolus) injection in less than one minute. Do not administer by intravenous infusion or in conjunction with other drug solutions.

HOW SUPPLIED

ORTHOCLONE OKT3 is supplied as a sterile solution in packages of 5 ampules (NDC 59676-101-01). Each 5 mL ampule contains 5 mg of muromonab-CD3.

Storage: Store in a refrigerator at 2° to 8°C (36° to 46°F). DO NOT FREEZE OR SHAKE.

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PROCRIT®
EPOETIN ALFA
PROCRIT registered trademark of distributor
FOR INJECTION

DESCRIPTION

Erythropoietin is a glycoprotein which stimulates red blood cell production. It is produced in the kidney and stimulates the division and differentiation of committed erythroid progenitors in the bone marrow. PROCRIT (Epoetin alfa), a 165 amino acid glycoprotein manufactured by recombinant DNA technology, has the same biological effects as endogenous erythropoietin.[1] It has a molecular weight of 30,400 daltons and is produced by mammalian cells into which the human erythropoietin gene has been introduced. The product contains the identical amino acid sequence of isolated natural erythropoietin.

PROCRIT is formulated as a sterile, colorless, liquid in an isotonic sodium chloride/sodium citrate buffered solution for intravenous (IV) or subcutaneous (SC) administration.

Single-Dose, Preservative-Free Vial: 1 mL (2,000, 3,000, 4,000 or 10,000 Units/mL). Each 1 mL of solution contains 2,000, 3,000, 4,000 or 10,000 Units of Epoetin alfa, 2.5 mg Albumin (Human), 5.8 mg sodium citrate, 5.8 mg sodium chloride, and 0.06 mg citric acid in Water for Injection, USP (pH 6.9±0.3). This formulation contains no preservative.

Single-Dose, Preservative-Free Vial: 1 mL (40,000 Units/mL). Each 1 mL of solution contains 40,000 Units of Epoetin alfa, 2.5 mg Albumin (Human), 1.164 mg sodium phosphate monobasic monohydrate, 1.766 mg sodium phosphate dibasic anhydrate, 0.696 mg sodium citrate, 5.78 mg sodium chloride, and 6.8 mcg citric acid in Water for Injection, USP (pH 6.9±0.3). This formulation contains no preservative.

Multidose, Preserved Vial: 2 mL (20,000 Units, 10,000 Units/mL). Each 1 mL of solution contains 10,000 Units of citrate, 8.2 mg sodium chloride, 0.11 mg citric acid, and 1% benzyl alcohol as preservative in Water for Injection, USP (pH 6.1±0.3).

Multidose, Preserved Vial: 1 mL (20,000 Units/mL). Each 1 mL of solution contains 20,000 Units of Epoetin alfa, 2.5 mg Albumin (Human), 1.3 mg sodium citrate, 8.2 mg sodium chloride, 0.11 mg citric acid, and 1% benzyl alcohol as preservative in Water for Injection, USP (pH 6.1±0.3).

CLINICAL PHARMACOLOGY

Chronic Renal Failure Patients

Endogenous production of erythropoietin is normally regulated by the level of tissue oxygenation. Hypoxia and anemia generally increase the production of erythropoietin, which in turn stimulates erythropoiesis.[2] In normal subjects, plasma erythropoietin levels range from 0.01 to 0.03 Units/mL[2,3] and increase up to 100- to 1000-fold during hypoxia or anemia.[2,3] In contrast, in patients with chronic renal failure (CRF), production of erythropoietin is impaired, and this erythropoietin deficiency is the primary cause of their anemia.[3,4]

Chronic renal failure is the clinical situation in which there is a progressive and usually irreversible decline in kidney function. Such patients may manifest the sequelae of renal dysfunction, including anemia, but do not necessarily require regular dialysis. Patients with end-stage renal disease (ESRD) are those patients with CRF who require regular dialysis or kidney transplantation for survival.

PROCRIT has been shown to stimulate erythropoiesis in anemic patients with CRF, including both patients on dialysis and those who do not require regular dialysis.[4-13] The first evidence of a response to the three times weekly (T.I.W.) administration of PROCRIT is an increase in the reticulocyte count within 10 days, followed by increases in the red cell count, hemoglobin, and hematocrit, usually within 2-6 weeks.[4,5] Because of the length of time required for erythropoiesis — several days for erythroid progenitors to mature and be released into the circulation — a clinically significant increase in hematocrit is usually not observed in less than 2 weeks and may require up to 6 weeks in some patients. Once the hematocrit reaches the suggested target range (30-36%), that level can be sustained by PROCRIT therapy in the absence of iron deficiency and concurrent illnesses.

The rate of hematocrit increase varies between patients and is dependent upon the dose of PROCRIT, within a therapeutic range of approximately 50-300 Units/kg (T.I.W.).[4] A greater biologic response is not observed at doses exceeding 300 Units/kg (T.I.W.).[6] Other factors affecting the rate and extent of response include availability of iron stores, the baseline hematocrit, and the presence of concurrent medical problems.

Zidovudine-treated HIV-infected Patients

Responsiveness to PROCRIT in HIV-infected patients is dependent upon the endogenous serum erythropoietin level prior to treatment. Patients with endogenous serum erythropoietin levels ≤ 500 mUnits/mL, and who are receiving a dose of zidovudine ≤ 4,200 mg/week, may respond to PROCRIT therapy. Patients with endogenous serum erythropoietin levels > 500 mUnits/mL do not appear to respond to PROCRIT therapy. In a series of four clinical trials involving 255 patients, 60% to 80% of HIV-infected patients treated with zidovudine had endogenous serum erythropoietin levels ≤ 500 mUnits/mL.

Response to PROCRIT in zidovudine-treated, HIV-infected patients is manifested by reduced transfusion requirements and increased hematocrit.

Cancer Patients on Chemotherapy

Anemia in cancer patients may be related to the disease itself or the effect of concomitantly administered chemotherapeutic agents. PROCRIT has been shown to increase hematocrit and decrease transfusion requirements after the first month of therapy (months 2 and 3), in anemic cancer patients undergoing chemotherapy.

A series of clinical trials enrolled 131 anemic cancer patients who were receiving cyclic cisplatin- or non cisplatin-containing chemotherapy. Endogenous baseline serum erythropoietin levels varied among patients in these trials with approximately 75% (N=83/110) having endogenous serum erythropoietin levels ≤ 132 mUnits/mL, and approximately 4% (N=4/110) of patients having endogenous serum erythropoietin levels > 500 mUnits/mL. In general, patients with lower baseline serum erythropoietin levels responded more vigorously to PROCRIT than patients with higher baseline erythropoietin levels. Although no specific serum erythropoietin level can be stipulated above which patients would be unlikely to respond to PROCRIT therapy, treatment of patients with grossly elevated serum erythropoietin levels (e.g., > 200 mUnits/mL) is not recommended.

Pharmacokinetics

Intravenously administered PROCRIT is eliminated at a rate consistent with first order kinetics with a circulating half-life ranging from approximately 4 to 13 hours in patients with CRF. Within the therapeutic dose range, detectable levels of plasma erythropoietin are maintained for at least 24 hours.[7] After subcutaneous administration of PROCRIT to patients with CRF, peak serum levels are achieved within 5-24 hours after administration and decline slowly thereafter. There is no apparent difference in half-life between patients not on dialysis whose serum creatinine levels were greater than 3, and patients maintained on dialysis.

In normal volunteers, the half-life of intravenously administered PROCRIT is approximately 20% shorter than the half-life in CRF patients. The pharmacokinetics of PROCRIT have not been studied in HIV-infected patients. It has been demonstrated in normal volunteers that the 10,000 U/mL citrate-buffered Epoetin alfa formulation and the 40,000 U/mL phosphate-buffered Epoetin alfa formulation are bioequivalent after subcutaneous administration of single 750 Units/kg doses. The C_{max} and $t_{½}$ after administration of the phosphate buffered Epoetin alfa formulation were 1.80 ± 0.7 U/mL and 19.0 ± 5.9 hours (mean ± SD), respectively. The corresponding mean ± SD values for the citrate-buffered Epoetin alfa formulation were 2 ± 0.9 U/mL and 16.3 ± 3.9 hours. There was minimal accumulation in serum after two weekly 750 Units/kg subcutaneous doses of Epoetin alfa.

INDICATIONS AND USAGE

Treatment of Anemia of Chronic Renal Failure Patients

PROCRIT is indicated in the treatment of anemia associated with chronic renal failure, including patients on dialysis (end-stage renal disease) and patients not on dialysis. PROCRIT is indicated to elevate or maintain the red blood cell level (as manifested by the hematocrit or hemoglobin determinations) and to decrease the need for transfusions in these patients.

Non-dialysis patients with symptomatic anemia considered for therapy should have a hematocrit less than 30%.

PROCRIT is not intended for patients who require immediate correction of severe anemia. PROCRIT may obviate the need for maintenance transfusions but is not a substitute for emergency transfusion.

Prior to initiation of therapy, the patient's iron stores should be evaluated. Transferrin saturation should be at least 20% and ferritin at least 100 ng/mL. Blood pressure should be adequately controlled prior to initiation of PROCRIT therapy, and must be closely monitored and controlled during therapy.

PROCRIT should be administered under the guidance of a qualified physician (see "DOSAGE and ADMINISTRATION").

Treatment of Anemia in Zidovudine-treated HIV-infected Patients

PROCRIT is indicated for the treatment of anemia related to therapy with zidovudine in HIV-infected patients. PROCRIT is indicated to elevate or maintain the red blood cell level (as manifested by the hematocrit or hemoglobin determinations) and to decrease the need for transfusions in these patients. PROCRIT is not indicated for the treatment of anemia in HIV-infected patients due to other factors such as iron or folate deficiencies, hemolysis or gastrointestinal bleeding, which should be managed appropriately.

PROCRIT, at a dose of 100 Units/kg three times per week, is effective in decreasing the transfusion requirement and increasing the red blood cell level of anemic, HIV-infected patients treated with zidovudine, when the endogenous serum erythropoietin level is ≤ 500 mUnits/mL and when patients are receiving a dose of zidovudine ≤ 4,200 mg/week.

Treatment of Anemia in Cancer Patients on Chemotherapy

PROCRIT is indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy. PROCRIT is indicated to decrease the need for transfusions in patients who will be receiving concomitant chemotherapy for a minimum of 2 months. PROCRIT is not indicated for the treatment of anemia in cancer patients due to other factors such as iron or folate deficiencies, hemolysis or gastrointestinal bleeding which should be managed appropriately.

Reduction of Allogeneic Blood Transfusion in Surgery Patients

PROCRIT is indicated for the treatment of anemic patients (hemoglobin >10 to ≤13 g/dL) scheduled to undergo elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusions.[14-15] PROCRIT is indicated for patients at high risk for perioperative transfusions with significant, anticipated blood loss. PROCRIT is not indicated for anemic patients who are willing to donate autologous blood. The safety of the perioperative use of PROCRIT has been studied only in patients who are receiving anticoagulant prophylaxis.

Clinical Experience: Response to PROCRIT

Chronic Renal Failure Patients

Response to PROCRIT was consistent across all studies. In the presence of adequate iron stores (see "Iron Evaluation"), the time to reach the target hematocrit is a function of the baseline hematocrit and the rate of hematocrit rise.

The rate of increase in hematocrit is dependent upon the dose of PROCRIT administered and individual patient variation. In clinical trials at starting doses of 50-150 Units/kg (T.I.W.), patients responded with an average rate of hematocrit rise of:

HEMATOCRIT INCREASE

STARTING DOSE (T.I.W. IV)	POINTS/DAY	POINTS/ 2 WEEKS
50 Units/kg	0.11	1.5
100 Units/kg	0.18	2.5
150 Units/kg	0.25	3.5

Over this dose range, approximately 95% of all patients responded with a clinically significant increase in hematocrit, and by the end of approximately 2 months of therapy virtually all patients were transfusion-independent. Changes in

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rocrit—Cont.

e quality of life of patients treated with PROCRIT were sessed as part of a Phase III clinical trial.[5,6] Once the tar- t hematocrit (32-38%) was achieved, statistically signifi- nt improvements were demonstrated for most quality of e parameters measured, including energy and activity vel, functional ability, sleep and eating behavior, health atus, satisfaction with health, sex life, well-being, psycho- gical effect, life satisfaction, and happiness. Patients also ported improvement in their disease symptoms. They owed a statistically significant increase in exercise capac- y (VO_2 max), energy, and strength with a significant re- uction in aching, dizziness, anxiety, shortness of breath, uscle weakness, and leg cramps.[8,17]

atients On Dialysis: Thirteen clinical studies were con- ucted, involving intravenous administration to a total of ,010 anemic patients on dialysis for 986 patient-years of ROCRIT therapy. In the three largest of these clinical tri- ls, the median maintenance dose necessary to maintain ie hematocrit between 30-36% was approximately 75 nits/kg (T.I.W.). In the U.S. multicenter Phase III study, pproximately 65% of the patients required doses of 100 nits/kg (T.I.W.), or less, to maintain their hematocrit at ap- roximately 35%. Almost 10% of patients required a dose f more than 200 Units/kg (T.I.W.) to maintain their hemat- crit at this level.

multicenter, unit dose study was also conducted in 119 pa- ients receiving peritoneal dialysis who self-administered PROCRIT subcutaneously for approximately 109 patient- ears of experience. Patients responded to PROCRIT ad- ministered subcutaneously in a manner similar to patients eceiving intravenous administration.[18]

Patients With CRF Not Requiring Dialysis: Four clinical rials were conducted in patients with CRF not on dialysis nvolving 181 patients treated with PROCRIT for approxi- nately 67 patient-years of experience. These patients re- sponded to PROCRIT therapy in a manner similar to that bserved in patients on dialysis. Patients with CRF not on dialysis demonstrated a dose-dependent and sustained in- crease in hematocrit when PROCRIT was administered by either an intravenous (IV) or subcutaneous (SC) route, with similar rates of rise of hematocrit when PROCRIT was ad- ministered by either route. Moreover, PROCRIT doses of 75-150 Units/kg per week have been shown to maintain hema- tocrits of 36-38% for up to six months. Correcting the ane- mia of progressive renal failure will allow patients to remain active even though their renal function continues to decrease.[19–21]

Zidovudine-treated HIV-infected Patients

PROCRIT has been studied in four placebo-controlled trials enrolling 297 anemic (hematocrit < 30%) HIV-infected (AIDS) patients receiving concomitant therapy with zidovu- dine, (all patients were treated with Epoetin alfa manufac- tured by Amgen Inc.). In the subgroup of patients (89/125 PROCRIT, and 88/130 placebo) with prestudy endogenous serum erythropoietin levels ≤ 500 mUnits/mL PROCRIT reduced the mean cumulative number of units of blood transfused per patient by approximately 40%, as compared to the placebo group.[22] Among those patients who required transfusions at baseline, 43% of patients treated with PROCRIT versus 18% of placebo-treated patients were transfusion-independent during the second and third months of therapy. PROCRIT therapy also resulted in sig- nificant increases in hematocrit in comparison to placebo. When examining the results according to the weekly dose of zidovudine received during Month 3 of therapy, there was a statistically significant ($p < 0.003$) reduction in transfusion requirements in patients treated with PROCRIT (N=51) compared to placebo-treated patients (N=54) whose mean weekly zidovudine dose was ≤ 4,200 mg/week.[22]

Approximately 17% of the patients with endogenous serum erythropoietin levels ≤ 500 mUnits/mL receiving PROCRIT in doses from 100-200 Units/kg three times weekly (T.I.W.) achieved a hematocrit of 38% without administration of transfusions or a significant reduction in zidovudine dose. In the subgroup of patients whose prestudy endogenous serum erythropoietin levels were > 500 mUnits/mL, PROCRIT therapy did not reduce transfusion requirements or increase hematocrit, compared to the corresponding re- sponses in placebo-treated patients.

In a six month open-label PROCRIT study, patients re- sponded with decreased transfusion requirements and sus- tained increases in hematocrit and hemoglobin with doses of PROCRIT up to 300 Units/kg (T.I.W.).[21–23]

Responsiveness to PROCRIT therapy may be blunted by in- tercurrent infectious/inflammatory episodes and by an in- crease in zidovudine dosage. Consequently, the dose of PROCRIT must be titrated based on these factors to main- tain the desired erythropoietic response.

Cancer Patients on Chemotherapy

PROCRIT has been studied in a series of placebo-controlled, double-blind trials in a total of 131 anemic cancer patients. Within this group, 72 patients were treated with concomi- tant noncisplatin-containing chemotherapy regimens and 59 patients were treated with concomitant cisplatin-con- taining chemotherapy regimens. Patients were randomized to PROCRIT 150 Units/kg or placebo subcutaneously (T.I.W.) for 12 weeks.

PROCRIT therapy was associated with a significantly ($p<0.008$) greater hematocrit response than in the corre- sponding placebo-treated patients (see TABLE).[22]

HEMATOCRIT (%): MEAN CHANGE FROM BASELINE TO FINAL VALUE[a]

STUDY	PROCRIT	PLACEBO
Chemotherapy	7.6	1.3
Cisplatin	6.9	0.6

[a] Significantly higher in PROCRIT patients than in placebo patients ($p < 0.008$)

In the two types of chemotherapy studies [utilizing a PROCRIT dose of 150 Units/kg (T.I.W.)] the mean number of units of blood transfused per patient after the first month of therapy was significantly ($p < 0.02$) lower in patients treated with PROCRIT (0.71 units in Months 2, 3) than in corresponding placebo-treated patients (1.84 units in Months 2, 3). Moreover, the proportion of patients trans- fused during Months 2 and 3 of therapy combined was sig- nificantly ($p < 0.03$) lower in the patients treated with PROCRIT than in the corresponding placebo-treated pa- tients (22% versus 43%).[22]

Comparable intensity of chemotherapy in the PROCRIT and placebo groups in the chemotherapy trials was sug- gested by a similar area under the neutrophil time curve in patients treated with PROCRIT and placebo-treated pa- tients as well as by a similar proportion of patients in groups treated with PROCRIT and placebo-treated groups whose absolute neutrophil counts fell below 1,000 cells/μL. Available evidence suggests that patients with lymphoid and solid cancers respond equivalently to PROCRIT therapy, and that patients with or without tumor infiltra- tion of the bone marrow respond equivalently to PROCRIT therapy.

Surgery Patients

PROCRIT has been studied in a placebo-controlled, double- blind trial enrolling 316 patients scheduled for major, elec- tive orthopedic hip or knee surgery who were expected to require ≥2 units of blood and who were not able or willing to participate in an autologous blood donation program. Based on previous studies which demonstrated that pre- treatment hemoglobin is a predictor of risk of receiving transfusion[16,24], patients were stratified into one of three groups based on their pretreatment hemoglobin [≤10 (n=2), >10 to ≤13 (n=96), and >13 to ≤15 g/dL (n=218)] and then randomly assigned to receive 300 U/kg PROCRIT, 100 U/kg PROCRIT or placebo by subcutaneous injection for 10 days before surgery, on the day of surgery, and for four days after surgery[14]. All patients received oral iron and a low dose postoperative warfarin regimen.[14]

Treatment with PROCRIT 300 U/kg significantly (p=0.024) reduced the risk of allogeneic transfusion in patients with a pretreatment hemoglobin of >10 to ≤13 g/dL; 5/31 (16%) of PROCRIT 300 U/kg, 6/26 (23%) of PROCRIT 100 U/kg and 13/29 (45%) of placebo-treated patients were transfused.[14] There was no significant difference in the number of patients transfused between PROCRIT (9% 300 U/kg, 6% 100 U/kg) and placebo (13%) in the >13 to ≤15 g/dL hemoglobin stratum. There were too few patients in the ≤10 g/dL group to determine if PROCRIT is useful in this hemoglobin strata.

In the >10 to ≤13 g/dL pretreatment stratum, the mean number of units transfused per PROCRIT-treated patient (0.45 units blood for 300 U/kg, 0.42 units blood for 100 U/kg) was less than the mean transfused per placebo-treated patient (1.14 units) (overall p=0.028). In addition, mean hemoglobin, hematocrit and reticulocyte counts increased significantly during the presurgery period in PROCRIT-treated patients.[14]

PROCRIT was also studied in an open-label, parallel-group trial enrolling 145 subjects with a pretreatment hemoglobin level of ≥10 to ≤13 g/dL who were scheduled for major or- thopedic hip or knee surgery and who were not participat- ing in an autologous program.[15] Subjects were randomly as- signed to receive one of two subcutaneous dosing regimens of PROCRIT (600 U/kg once weekly for three weeks prior to surgery and on the day of surgery or 300 U/kg once daily for 10 days prior to surgery, on the day of surgery and for four days after surgery). All subjects received oral iron and ap- propriate pharmacologic anticoagulation therapy.

From pretreatment to presurgery, the mean increase in he- moglobin in 600 U/kg weekly group (1.44 g/dL) was greater than observed in the 300 U/kg daily group.[15] The mean in- crease in absolute reticulocyte count was smaller in the weekly group ($0.11 \times 10^6/mm^3$) compared to the daily group ($0.17 \times 10^6/mm^3$). Mean hemoglobin levels were similar for the two treatment groups throughout the postsurgical period.

The erythropoietic response observed in both treatment groups resulted in similar transfusion rates [11/69 (16%) in the 600 U/kg weekly group and 14/71 (20%) in the 300 U/kg daily group].[15] The mean number of units transfused per subject was approximately 0.3 units in both treatment groups.

CONTRAINDICATIONS

PROCRIT is contraindicated in patients with:

1) Uncontrolled hypertension.
2) Known hypersensitivity to mammalian cell-derived products.
3) Known hypersensitivity to Albumin (Human).

WARNINGS

Pediatric Use:

The multidose preserved formulation contains benzyl alco- hol. Benzyl alcohol has been reported to be associated with an increased incidence of neurological and other complica- tions in premature infants which are sometimes fatal. The safety and effectiveness of Epoetin alfa in children have not been established.

Thrombotic Events and Increased Mortality

A randomized, prospective trial of 1265 hemodialysis pa- tients with clinically evident cardiac disease (ischemic heart disease or congestive heart failure) was conducted in which patients were assigned to PROCRIT treatment targeted to a maintenance hematocrit of either 42 ± 3% or 30 ± 3%. Increased mortality was observed in 634 patients random- ized to a target hematocrit of 42% [221 deaths (35% mortal- ity)] compared to 631 patients targeted to remain at a he- matocrit of 30% [185 deaths (29% mortality)]. The reason for increased mortality observed in these studies is un- known, however the incidence of non-fatal myocardial infarctions (3.1% vs. 2.3%), vascular access thrombosis (39% vs. 29%) and all other thrombotic events (22% vs. 18%) were also higher in the group randomized to achieve a he- matocrit of 42%.

Increased mortality was observed in a randomized placebo- controlled study of PROCRIT in patients who did not have chronic renal failure who were undergoing coronary artery bypass surgery (7 deaths in 126 patients randomized to PROCRIT vs. no deaths among 56 patients receiving place- bo). Four of these deaths occurred during the period of study drug administration and all 4 deaths were associated with thrombotic events. While the extent of the population af- fected is unknown, in patients at risk for thrombosis, the anticipated benefits of PROCRIT treatment should be weighed against the potential for increased risks associated with therapy.

Chronic Renal Failure Patients

Hypertension: Patients with uncontrolled hypertension should not be treated with PROCRIT; blood pressure should be controlled adequately before initiation of therapy. Up to 80% of patients with CRF have a history of hypertension.[25] Although there does not appear to be any direct pressor ef- fects of PROCRIT, blood pressure may rise during PROCRIT therapy. During the early phase of treatment when the hematocrit is increasing, approximately 25% of patients on dialysis may require initiation of, or increases in, antihypertensive therapy. Hypertensive encephalopathy and seizures have been observed in patients with CRF treated with PROCRIT.

Special care should be taken to closely monitor and aggres- sively control blood pressure in patients treated with PROCRIT. Patients should be advised as to the importance of compliance with antihypertensive therapy and dietary re- strictions. If blood pressure is difficult to control by initia- tion of appropriate measures, the hematocrit may be re- duced by decreasing or withholding the dose of PROCRIT. A clinically significant decrease in hematocrit may not be ob- served for several weeks.

It is recommended that the dose of PROCRIT be decreased if the hematocrit increase exceeds 4 points in any two-week period, because of the possible association of excessive rate of rise of hematocrit with an exacerbation of hypertension. In chronic renal failure patients on hemodialysis with clini- cally evident ischemic heart disease or congestive heart failure, the hematocrit should be managed carefully, not to exceed 36%. (see "Thrombotic Events")

Seizures: Seizures have occurred in patients with CRF participating in PROCRIT clinical trials.

In patients on dialysis, there was a higher incidence of sei- zures during the first 90 days of therapy (occurring in ap- proximately 2.5% of patients) as compared with later timepoints.

Given the potential for an increased risk of seizures during the first 90 days of therapy, blood pressure and the presence of premonitory neurologic symptoms should be monitored closely. Patients should be cautioned to avoid potentially hazardous activities such as driving or operating heavy ma- chinery during this period.

While the relationship between seizures and the rate of rise of hematocrit is uncertain, it is recommended that the dose of PROCRIT be decreased if the hematocrit increase exceeds 4 points in any two-week period.

Thrombotic Events: During hemodialysis, patients treated with PROCRIT may require increased anticoagula- tion with heparin to prevent clotting of the artificial kidney. (See "ADVERSE REACTIONS" for more information about thrombotic events.)

Other thrombotic events (e.g., myocardial infarction, cere- brovascular accident, transient ischemic attack) have oc- curred in clinical trials at an annualized rate of less than 0.04 events per patient-year of PROCRIT therapy. These trials were conducted in patients with CRF (whether on di- alysis or not) in whom the target hematocrit was 32-40%. However, the risk of thrombotic events, including vascular access thromboses, was significantly increased in patients with ischemic heart disease or congestive heart failure re- ceiving PROCRIT therapy with the goal of reaching a nor- mal hematocrit (42%) as compared to a target hematocrit of 30%. Patients with pre-existing cardiovascular disease should be monitored closely.

Zidovudine-treated HIV-infected Patients

In contrast to CRF patients, PROCRIT therapy has not been linked to exacerbation of hypertension, seizures, and thrombotic events in HIV-infected patients.

PRECAUTIONS

The parenteral administration of any biologic product should be attended by appropriate precautions in case aller-

gic or other untoward reactions occur (see "CONTRAINDICATIONS"). In clinical trials, while transient rashes were occasionally observed concurrently with PROCRIT therapy, no serious allergic or anaphylactic reactions were reported. See "ADVERSE REACTIONS" for more information regarding allergic reactions.

The safety and efficacy of PROCRIT therapy have not been established in patients with a known history of a seizure disorder or underlying hematologic disease (e.g., sickle cell anemia, myelodysplastic syndromes, or hypercoagulable disorders).

In some female patients, menses have resumed following PROCRIT therapy; the possibility of pregnancy should be discussed and the need for contraception evaluated.

Hematology: Exacerbation of porphyria has been observed rarely in patients with CRF treated with PROCRIT. However, PROCRIT has not caused increased urinary excretion of porphyrin metabolites in normal volunteers, even in the presence of a rapid erythropoietic response. Nevertheless, PROCRIT should be used with caution in patients with known porphyria.

In preclinical studies in dogs and rats, but not in monkeys, PROCRIT therapy was associated with subclinical bone marrow fibrosis. Bone marrow fibrosis is a known complication of CRF in humans and may be related to secondary hyperparathyroidism or unknown factors. The incidence of bone marrow fibrosis was not increased in a study of patients on dialysis who were treated with PROCRIT for 12-19 months, compared to the incidence of bone marrow fibrosis in a matched group of patients who had not been treated with PROCRIT.

Hematocrit in CRF patients should be measured twice a week; zidovudine-treated HIV-infected and cancer patients should have hematocrit measured once a week until hematocrit has been stabilized, and measured periodically thereafter.

Delayed or Diminished Response: If the patient fails to respond or to maintain a response to doses within the recommended dosing range, the following etiologies should be considered and evaluated:

1) Iron deficiency: Virtually all patients will eventually require supplemental iron therapy. (See "Iron Evaluation").
2) Underlying infectious, inflammatory, or malignant processes.
3) Occult blood loss.
4) Underlying hematologic diseases (i.e., thalassemia, refractory anemia, or other myelodysplastic disorders).
5) Vitamin deficiencies: folic acid or vitamin B12.
6) Hemolysis.
7) Aluminum intoxication.
8) Osteitis fibrosa cystica.

Iron Evaluation: During PROCRIT therapy, absolute or functional iron deficiency may develop. Functional iron deficiency, with normal ferritin levels but low transferrin saturation, is presumably due to the inability to mobilize iron stores rapidly enough to support increased erythropoiesis. Transferrin saturation should be at least 20% and ferritin should be at least 100 ng/mL.

Prior to and during PROCRIT therapy, the patient's iron status, including transferrin saturation (serum iron divided by iron binding capacity) and serum ferritin, should be evaluated. Virtually all patients will eventually require supplemental iron to increase or maintain transferrin saturation to levels which will adequately support erythropoiesis stimulated by PROCRIT. All surgery patients being treated with PROCRIT should receive adequate iron supplementation throughout the course of therapy in order to support erythropoiesis and avoid depletion of iron stores.

Drug Interactions: No evidence of interaction of PROCRIT with other drugs was observed in the course of clinical trials.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Carcinogenic potential of PROCRIT has not been evaluated. PROCRIT does not induce bacterial gene mutation (Ames Test), chromosomal aberrations in mammalian cells, micronuclei in mice, or gene mutation at the HGPRT locus. In female rats treated intravenously with PROCRIT, there was a trend for slightly increased fetal wastage at doses of 100 and 500 Units/kg.

Pregnancy Category C: PROCRIT has been shown to have adverse effects in rats when given in doses five times the human dose. There are no adequate and well-controlled studies in pregnant women. PROCRIT should be used during pregnancy only if potential benefit justifies the potential risk to the fetus.

In studies in female rats, there were decreases in body weight gain, delays in appearance of abdominal hair, delayed eyelid opening, delayed ossification, and decreases in the number of caudal vertebrae in the F1 fetuses of the 500 Units/kg group. In female rats treated intravenously, there was a trend for slightly increased fetal wastage at doses of 100 and 500 Units/kg. PROCRIT has not shown any adverse effect at doses as high as 500 Units/kg in pregnant rabbits (from day 6 to 18 of gestation).

Nursing Mothers: Postnatal observations of the live offspring (F1 generation) of female rats treated with PROCRIT during gestation and lactation revealed no effect of PROCRIT at doses of up to 500 Units/kg. There were, however, decreases in body weight gain, delays in appearance of abdominal hair, eyelid opening, and decreases in the number of caudal vertebrae in the F1 fetuses of the 500 Units/kg group. There were no effects related to PROCRIT on the F2 generation fetuses.

It is not known whether PROCRIT is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PROCRIT is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of PROCRIT in children have not been established (See "WARNINGS").

Chronic Renal Failure Patients

Patients with CRF Not Requiring Dialysis: Blood pressure and hematocrit should be monitored no less frequently than for patients maintained on dialysis. Renal function and fluid and electrolyte balance should be closely monitored, as an improved sense of well-being may obscure the need to initiate dialysis in some patients.

Hematology: Sufficient time should be allowed to determine a patient's responsiveness to a dosage of PROCRIT before adjusting the dose. Because of the time required for erythropoiesis and the red cell half-life, an interval of 2-6 weeks may occur between the time of a dose adjustment (initiation, increase, decrease, or discontinuation) and a significant change in hematocrit.

In order to avoid reaching the suggested target hematocrit too rapidly, or exceeding the suggested target range (hematocrit of 30-36%), the guidelines for dose and frequency of dose adjustments (see "DOSAGE AND ADMINISTRATION") should be followed.

For patients who respond to PROCRIT with a rapid increase in hematocrit (e.g., more than 4 points in any two-week period), the dose of PROCRIT should be reduced because of the possible association of excessive rate of rise of hematocrit with an exacerbation of hypertension.

The elevated bleeding time characteristic of CRF decreases toward normal after correction of anemia in patients treated with PROCRIT. Reduction of bleeding time also occurs after correction of anemia by transfusion.

Laboratory Monitoring: The hematocrit should be determined twice a week until it has stabilized in the suggested target range and the maintenance dose has been established. After any dose adjustment, the hematocrit should also be determined twice weekly for at least 2-6 weeks until it has been determined that the hematocrit has stabilized in response to the dose change. The hematocrit should then be monitored at regular intervals.

A complete blood count with differential and platelet count should be performed regularly. During clinical trials, modest increases were seen in platelets and white blood cell counts. While these changes were statistically significant, they were not clinically significant and the values remained within normal ranges.

In patients with CRF, serum chemistry values [including blood urea nitrogen (BUN), uric acid, creatinine, phosphorus, and potassium] should be monitored regularly. During clinical trials in patients on dialysis, modest increases were seen in BUN, creatinine, phosphorus, and potassium. In some patients with CRF not on dialysis, treated with PROCRIT, modest increases in serum uric acid and phosphorus were observed. While changes were statistically significant, the values remained within the ranges normally seen in patients with CRF.

Diet: As the hematocrit increases and patients experience an improved sense of well-being and quality of life, the importance of compliance with dietary and dialysis prescriptions should be reinforced. In particular, hyperkalemia is not uncommon in patients with CRF. In U.S. studies in patients on dialysis, hyperkalemia has occurred at an annualized rate of approximately 0.11 episodes per patient-year of PROCRIT therapy, often in association with poor compliance to medication, diet and/or dialysis.

Dialysis Management: Therapy with PROCRIT results in an increase in hematocrit and a decrease in plasma volume, which could affect dialysis efficiency. In studies to date, the resulting increase in hematocrit did not appear to adversely affect dialyzer function[9,10] or the efficiency of high flux hemodialysis.[11] During hemodialysis, patients treated with PROCRIT may require increased anticoagulation with heparin to prevent clotting of the artificial kidney.

Patients who are marginally dialyzed may require adjustments in their dialysis prescription. As with all patients on dialysis, the serum chemistry values (including BUN, creatinine, phosphorus, and potassium) in patients treated with PROCRIT should be monitored regularly to assure the adequacy of the dialysis prescription.

Information for Patients: In those situations in which the physician determines that a home dialysis patient can safely and effectively self-administer PROCRIT, the patient should be instructed as to the proper dosage and administration. Home dialysis patients should be referred to the full "INFORMATION FOR HOME DIALYSIS PATIENTS" section attached; it is not a disclosure of all possible effects. Patients should be informed of the signs and symptoms of allergic drug reaction and advised of appropriate actions. If home use is prescribed for a home dialysis patient, the patient should be thoroughly instructed in the importance of proper disposal and cautioned against the reuse of needles, syringes, or drug product. A puncture-resistant container for the disposal of used syringes and needles should be available to the patient. The full container should be disposed of according to the directions provided by the physician.

Renal Function: In patients with CRF not on dialysis, renal function and fluid and electrolyte balance should be closely monitored, as an improved sense of well-being may obscure the need to initiate dialysis in some patients. In patients with CRF not on dialysis, placebo-controlled studies of progression of renal dysfunction over periods of greater than one year have not been completed. In shorter-term trials in patients with CRF not on dialysis, changes in creatinine and creatinine clearance were not significantly different in patients treated with PROCRIT, compared with placebo-treated patients. Analysis of the slope of 1/serum creatinine vs. time plots in these patients indicates no significant change in the slope after the initiation of PROCRIT therapy.

Zidovudine-treated HIV-infected Patients

Hypertension: Exacerbation of hypertension has not been observed in zidovudine-treated HIV-infected patients treated with PROCRIT. However, PROCRIT should be withheld in these patients if pre-existing hypertension is uncontrolled, and should not be started until blood pressure is controlled. In double-blind studies, a single seizure has been experienced by a patient treated with PROCRIT.[22]

Cancer Patients on Chemotherapy

Hypertension: Hypertension, associated with a significant increase in hematocrit, has been noted rarely in cancer patients treated with PROCRIT. Nevertheless, blood pressure in patients treated with PROCRIT should be monitored carefully, particularly in patients with an underlying history of hypertension or cardiovascular disease.

Seizures: In double-blind, placebo-controlled trials, 3.2% (N=2/63) of patients treated with PROCRIT and 2.9% (N=2/68) of placebo-treated patients had seizures. Seizures in 1.6% (N=1/63) of patients treated with PROCRIT occurred in the context of a significant increase in blood pressure and hematocrit from baseline values. However, both patients treated with PROCRIT also had underlying CNS pathology which may have been related to seizure activity.

Thrombotic Events: In double-blind, placebo-controlled trials, 3.2% (N=2/63) of patients treated with PROCRIT and 11.8% (N=8/68) of placebo-treated patients had thrombotic events (e.g. pulmonary embolism, cerebrovascular accident).

Growth Factor Potential: PROCRIT is a growth factor that primarily stimulates red cell production. However, the possibility that PROCRIT can act as a growth factor for any tumor type, particularly myeloid malignancies, cannot be excluded.

Surgery Patients

Thrombotic/Vascular Events: In perioperative clinical trials with orthopedic patients, the overall incidence of thrombotic/vascular events was similar in Epoetin alfa and placebo-treated patients who had a pretreatment hemoglobin of >10 to ≤13 g/dL. In patients with a hemoglobin of >13 g/dL treated with 300 U/kg of Epoetin alfa, the possibility that PROCRIT treatment may be associated with an increased risk of postoperative thrombotic/vascular events cannot be excluded.[14-16,24]

In one study in which Epoetin alfa was administered in the perioperative period to patients undergoing coronary artery bypass graft surgery, there were seven deaths in the Epoetin alfa-treated groups (N=126) and no deaths in the placebo-treated group (N=56). Among the seven deaths in the Epoetin alfa-treated patients, four were at the time of therapy (between study day 2 and 8). The four deaths at the time of therapy (3%) were associated with thrombotic/vascular events. A causative role of Epoetin alfa cannot be excluded. (See "WARNINGS")

Hypertension: Blood pressure may rise in the perioperative period in patients being treated with PROCRIT. Therefore, blood pressure should be monitored carefully.

ADVERSE REACTIONS

Chronic Renal Failure Patients

Studies analyzed to date indicate that PROCRIT is generally well-tolerated. The adverse events reported are frequent sequelae of CRF and are not necessarily attributable to PROCRIT therapy. In double-blind, placebo-controlled studies involving over 300 patients with CRF, the events reported in greater than 5% of patients treated with PROCRIT during the blinded phase were:

PERCENT OF PATIENTS REPORTING EVENT

Event	Patients Treated with epoetin alfa (N=200)	PLACEBO-Treated Patients (N=135)
Hypertension	24%	19%
Headache	16%	12%
Arthralgias	11%	6%
Nausea	11%	9%
Edema	9%	10%
Fatigue	9%	14%
Diarrhea	9%	6%
Vomiting	8%	5%
Chest Pain	7%	9%
Skin Reaction (Administration Site)	7%	12%
Asthenia	7%	12%
Dizziness	7%	13%
Clotted Access	7%	2%

Significant adverse events of concern in patients with CRF treated in double-blinded, placebo-controlled trials occurred

Continued on next page

Procrit—C nt.

in the following percent of patients during the blinded phase of the studies:

Seizure	1.1%	1.1%
CVA / TIA	0.4%	0.6%
MI	0.4%	1.1%
Death	0	1.7%

In the U.S. PROCRIT studies in patients on dialysis (over 567 patients), the incidence (number of events per patient-year) of the most frequently reported adverse events were: hypertension (0.75), headache (0.40), tachycardia (0.31), nausea/vomiting (0.26), clotted vascular access (0.25), shortness of breath (0.14), hyperkalemia (0.11), and diarrhea (0.11). Other reported events occurred at a rate of less than 0.10 events per patient per year.

Events reported to have occurred within several hours of administration of PROCRIT were rare, mild, and transient, and included injection site stinging in dialysis patients and flu-like symptoms such as arthralgias and myalgias.

In all studies analyzed to date, PROCRIT administration was generally well-tolerated, irrespective of the route of administration.

Hypertension: Increases in blood pressure have been reported in clinical trials, often during the first 90 days of therapy. On occasion, hypertensive encephalopathy and seizures have been observed in patients with CRF treated with PROCRIT. When data from all patients in the U.S. Phase III multicenter trial were analyzed, there was an apparent trend of more reports of hypertensive adverse events in patients on dialysis with a faster rate of rise of hematocrit (greater than 4 hematocrit points in any two-week period). However, in a double-blind, placebo-controlled trial, hypertensive adverse events were not reported at an increased rate in the group treated with PROCRIT (150 Units/kg T.I.W.) relative to the placebo group.

Seizures: There have been 47 seizures in 1,010 patients on dialysis treated with PROCRIT in clinical trials, with an exposure of 986 patient-years for a rate of approximately 0.048 events per patient-year. However, there appeared to be a higher rate of seizures during the first 90 days of therapy (occurring in approximately 2.5% of patients) when compared to subsequent 90-day periods. The baseline incidence of seizures in the untreated dialysis population is difficult to determine; it appears to be in the range of 5-10% per patient-year.[26-28]

Thrombotic Events: In clinical trials where the maintenance hematocrit was 35 ± 3% on PROCRIT, clotting of the vascular access (A-V shunt) has occurred at an annualized rate of about 0.25 events per patient-year, and other thrombotic events (myocardial infarction, cerebrovascular accident, transient ischemic attack, and pulmonary embolism) occurred at a rate of 0.04 events per patient-year. In a separate study of 1,111 untreated dialysis patients, clotting of the vascular access occurred at a rate of 0.5 events per patient-year. However, in chronic renal failure patients on hemodialysis who also had clinically evident ischemic heart disease or congestive heart failure, the risk of A-V shunt thrombosis was higher (39% vs 29%, $p<0.001$), and myocardial infarction, vascular ischemic events, and venous thrombosis were increased in patients targeted to a hematocrit of 42 ± 3% compared to those maintained at 30 ± 3%. (see "WARNINGS")

In patients treated with commercial PROCRIT, there have been rare reports of serious or unusual thrombo-embolic events including migratory thrombophlebitis, microvascular thrombosis, pulmonary embolus, and thrombosis of the retinal artery, and temporal and renal veins. A causal relationship has not been established.

Allergic Reactions: There have been no reports of serious allergic reactions or anaphylaxis associated with PROCRIT administration during clinical trials. Skin rashes and urticaria have been observed rarely and when reported have generally been mild and transient in nature.

In over 125,000 patients treated with commercial PROCRIT, there have been rare reports of potentially serious allergic reactions including urticaria with associated respiratory symptoms or circumoral edema (<0.0001 events per patient-year), or urticaria alone (<0.0001 events per patient-year). Most reactions occurred in situations where a casual relationship could not be established. Many of these patients resumed PROCRIT therapy without recurrence of symptoms, some in conjunction with antihistamine pretreatment. However, symptoms recurred with rechallenge in a few instances, suggesting that allergic reactivity, although rare, may occasionally be associated with PROCRIT therapy.

There has been no evidence for development of antibodies to erythropoietin in patients tested to date, including those receiving PROCRIT for over 4 years. Nevertheless, if an anaphylactoid reaction occurs, PROCRIT should be immediately discontinued and appropriate therapy initiated.

Zidovudine-treated HIV-infected Patients

Adverse events reported in clinical trials with PROCRIT in zidovudine-treated HIV-infected patients were consistent with the progression of HIV infection. In double-blind, placebo-controlled studies of three-months duration involving approximately 300 zidovudine-treated HIV-infected patients, adverse events with an incidence of ≥10% in either patients treated with PROCRIT or placebo-treated patients were:

Percent of Patients Reporting Event

Event	Patients Treated with PROCRIT (N=144)	PLACEBO-Treated Patients (N=153)
Pyrexia	38%	29%
Fatigue	25%	31%
Headache	19%	14%
Cough	18%	14%
Diarrhea	16%	18%
Rash	16%	8%
Congestion, Respiratory	15%	10%
Nausea	15%	12%
Shortness of Breath	14%	13%
Asthenia	11%	14%
Skin Reaction, (Administration Site)	10%	7%
Dizziness	9%	10%

There were no statistically significant differences between treatment groups in the incidence of the above events.

In the 297 patients studied, PROCRIT was not associated with significant increases in opportunistic infections or mortality.[22] In 71 patients from this group treated with PROCRIT at 150 Units/kg (T.I.W.), serum p24 antigen levels did not appear to increase.[23] Preliminary data showed no enhancement of HIV replication in infected cell lines *in vitro*.[22]

Peripheral white blood cell and platelet counts are unchanged following PROCRIT therapy.

Allergic Reactions: Two zidovudine-treated HIV-infected patients had urticarial reactions within 48 hours of their first exposure to study medication. One patient was treated with PROCRIT and one was treated with placebo (PROCRIT vehicle alone). Both patients had positive immediate skin tests against their study medication with a negative saline control. The basis for this apparent pre-existing hypersensitivity to components of the PROCRIT formulation is unknown, but may be related to HIV-induced immunosuppression or prior exposure to blood products.

Seizures: In double-blind and open-label trials of PROCRIT in zidovudine-treated HIV-infected patients, ten patients have experienced seizures.[22] In general, these seizures appear to be related to underlying pathology such as meningitis or cerebral neoplasms, not PROCRIT therapy.

Cancer Patients on Chemotherapy

Adverse experiences reported in clinical trials with PROCRIT in cancer patients were consistent with the underlying disease state. In double-blind, placebo-controlled studies of up to 3-months duration involving 131 cancer patients, adverse events with an incidence >10% in either patients treated with PROCRIT or placebo-treated patients were as indicated below.

Percent of Patients Reporting Event

Event	Patients Treated with PROCRIT (N=63)	PLACEBO-Treated Patients (N=68)
Pyrexia	29%	19%
Diarrhea	21%[a]	7%
Nausea	17%[b]	32%
Vomiting	17%	15%
Edema	17%[c]	1%
Asthenia	13%	16%
Fatigue	13%	15%
Shortness of Breath	13%	9%
Paresthesia	11%	6%
Upper Respiratory Infection	11%	4%
Dizziness	5%	12%
Trunk Pain	3%[d]	16%

[a] $p = 0.041$ [c] $p = 0.0016$
[b] $p = 0.069$ [d] $p = 0.017$

Although some statistically significant differences between patients treated with PROCRIT and placebo-treated patients were noted, the overall safety profile of PROCRIT appeared to be consistent with the disease process of advanced cancer. During double-blind and subsequent open-label therapy in which patients (N=72 for total exposure to PROCRIT) were treated for up to 32 weeks with doses as high as 927 Units/kg, the adverse experience profile of PROCRIT was consistent with the progression of advanced cancer.

Based on comparable survival data and on the percentage of patients treated with PROCRIT and placebo-treated patients who discontinued therapy due to death, disease progression or adverse experiences (22% and 13%, respectively; $p = 0.25$), the clinical outcome in patients treated with PROCRIT and placebo-treated patients appeared to be similar. Available data from animal tumor models and measurement of proliferation of solid tumor cells from clinical biopsy specimens in response to PROCRIT suggest that PROCRIT does not potentiate tumor growth. Nevertheless, as a growth factor, the possibility that PROCRIT may potentiate growth of some tumors, particularly myeloid tumors, cannot be excluded. A randomized controlled Phase IV study is currently ongoing to further evaluate this issue.

The mean peripheral white blood cell count was unchanged following PROCRIT therapy compared to the corresponding value in the placebo-treated group.

Surgery Patients

Adverse events with an incidence of ≥10% are shown in the following table:

[See table below]

Thrombotic/vascular events: In three double-blind, placebo-controlled orthopedic surgery studies, the rate of deep venous thrombosis (DVT) was similar among Epoetin alfa and placebo-treated patients in the recommended population of patients with a pretreatment hemoglobin of >10 to ≤13 g/dL.[14,16,24] However, in 2 of 3 orthopedic surgery studies the overall rate (all pretreatment hemoglobin groups combined) of DVTs detected by postoperative ultrasonography and/or surveillance venography was higher in the Epoetin alfa-treated group than in the placebo-treated group (11% vs. 6%). This finding was attributable to the difference in DVT rates observed in the subgroup of patients with pretreatment hemoglobin >13 g/dL. However, the incidence of DVTs was within the range of that reported in the literature for orthopedic surgery patients.

In the orthopedic surgery study of patients with pretreatment hemoglobin of >10 to ≤13 g/dL which compared two dosing regimens (600 U/kg weekly × 4 and 300 U/kg daily × 15), four subjects in the 600 U/kg weekly PROCRIT group (5%) and no subjects in the 300 U/kg daily group had a thrombotic vascular event during the study period.[15]

In a study examining the use of Epoetin alfa in 182 patients scheduled for coronary artery bypass graft surgery, 23% of patients treated with Epoetin alfa and 29% treated with placebo experienced thrombotic/vascular events. There were 4 deaths among the Epoetin alfa-treated patients that were associated with a thrombotic/vascular event. A causative role of Epoetin alfa cannot be excluded. (See "WARNINGS")

Percent of Patients Reporting Event

Event	Patients Treated with PROCRIT 300 U/kg (N=112)[a]	Patients Treated with PROCRIT 100 U/kg (N=101)[a]	PLACEBO-Treated Patients (N=103)[a]	PROCRIT 600 U/kg (N=73)[b]	PROCRIT 300 U/kg (N=72)[b]
Pyrexia	51%	50%	60%	47%	42%
Nausea	48%	43%	45%	45%	58%
Constipation	43%	42%	43%	51%	53%
Skin Reaction, (Administration Site)	25%	19%	22%	26%	29%
Vomiting	22%	12%	14%	21%	29%
Skin Pain	18%	18%	17%	5%	4%
Pruritus	16%	16%	14%	14%	22%
Insomnia	13%	16%	13%	21%	18%
Headache	13%	11%	9%	10%	19%
Dizziness	12%	9%	12%	11%	21%
Urinary Tract Infection	12%	3%	11%	11%	8%
Hypertension	10%	11%	10%	5%	10%
Diarrhea	10%	7%	12%	10%	6%
Deep Venous Thrombosis	10%	3%	5%	0%[c]	0%[c]
Dyspepsia	9%	11%	6%	7%	8%
Anxiety	7%	2%	11%	11%	4%
Edema	6%	11%	8%	11%	7%

[a] Study including patients undergoing orthopedic surgery treated with PROCRIT or placebo for 15 days
[b] Study including patients undergoing orthopedic surgery treated with PROCRIT 600 U/kg weekly × 4 or 300 U/kg daily × 15

OVERDOSAGE

The maximum amount of PROCRIT that can be safely administered in single or multiple doses has not been determined. Doses of up to 1,500 Units/kg (T.I.W.) for three to four weeks have been administered without any direct toxic effects of PROCRIT itself.[6] Therapy with PROCRIT can re-

...ained and the dose appropriately adjusted. If the suggested target range is exceeded, PROCRIT may be temporarily withheld until the hematocrit returns to the suggested target range; PROCRIT therapy may then be resumed using a lower dose (see "DOSAGE AND ADMINISTRATION"). If polycythemia is of concern, phlebotomy may be indicated to decrease the hematocrit.

DOSAGE AND ADMINISTRATION

Chronic Renal Failure Patients

Starting doses of PROCRIT over the range of 50-100 Units/kg three times weekly (T.I.W.) have been shown to be safe and effective in increasing hematocrit and eliminating transfusion dependency in patients with CRF (see "Clinical Experience"). The dose of PROCRIT should be reduced as the hematocrit approaches 36% or increases by more than 4 points in any 2-week period. The dosage of PROCRIT must be individualized to maintain the hematocrit within the suggested target range. At the physician's discretion, the suggested target hematocrit range may be expanded to achieve maximal patient benefit.

PROCRIT may be given either as an intravenous (IV) or subcutaneous (SC) injection. In patients on hemodialysis, PROCRIT usually has been administered as an IV bolus (T.I.W.). While the administration of PROCRIT is independent of the dialysis procedure, PROCRIT may be administered into the venous line at the end of the dialysis procedure to obviate the need for additional venous access. In patients with CRF not on dialysis, PROCRIT may be given either as an IV or SC injection.

Home hemodialysis patients who have been judged competent by their physicians to self-administer PROCRIT without medical or other supervision may give themselves either an IV or SC injection. The table below provides general therapeutic guidelines for patients with CRF:

[See table above]

During therapy, hematological parameters should be monitored regularly (see "Laboratory Monitoring").

Pre-Therapy Iron Evaluation: Prior to and during PROCRIT therapy, the patient's iron stores, including transferrin saturation (serum iron divided by iron binding capacity) and serum ferritin, should be evaluated. Transferrin saturation should be at least 20%, and ferritin should be at least 100 ng/mL. Virtually all patients will eventually require supplemental iron to increase or maintain transferrin saturation to levels that will adequately support erythropoiesis stimulated by PROCRIT.

Dose Adjustment: Following PROCRIT therapy, a period of time is required for erythroid progenitors to mature and be released into circulation resulting in an eventual increase in hematocrit. Additionally, red blood cell survival time affects hematocrit and may vary due to uremia. As a result, the time required to elicit a clinically significant change in hematocrit (increase or decrease) following any dose adjustment may be 2-6 weeks.

Dose adjustment should not be made more frequently than once a month, unless clinically indicated. After any dose adjustment, the hematocrit should be determined twice weekly for at least 2-6 weeks (see "Laboratory Monitoring").

- If the hematocrit is increasing and approaching 36%, the dose should be reduced to maintain the suggested target hematocrit range. If the reduced dose does not stop the rise in hematocrit, and it exceeds 36%, doses should be temporarily withheld until the hematocrit begins to decrease, at which point therapy should be reinitiated at a lower dose.
- At any time, if the hematocrit increases by more than 4 points in a 2-week period, the dose should be immediately decreased. After the dose reduction, the hematocrit should be monitored twice weekly for 2-6 weeks, and further dose adjustments should be made as outlined in "Maintenance Dose".
- If a hematocrit increase of 5-6 points is not achieved after an 8-week period and iron stores are adequate (see "Delayed or Diminished Response"), the dose of PROCRIT may be incrementally increased. Further increases may be made at 4-6 week intervals until the desired response is attained.

Maintenance Dose: The maintenance dose must be individualized for each patient on dialysis. In the U.S. Phase III multicenter trial in patients on hemodialysis, the median maintenance dose was 75 Units/kg (T.I.W.), with a range from 12.5 to 525 Units/kg (T.I.W.). Almost 10% of the patients required a dose of 25 Units/kg, or less, and approximately 10% of the patients required more than 200 Units/kg (T.I.W.) to maintain their hematocrit in the suggested target range.

If the hematocrit remains below, or falls below, the suggested target range, iron stores should be re-evaluated. If the transferrin saturation is less than 20%, supplemental iron should be administered. If the transferrin saturation is greater than 20%, the dose of PROCRIT may be increased. Such dose increases should not be made more frequently than once a month, unless clinically indicated, as the response time of the hematocrit to a dose increase can be 2-6 weeks. Hematocrit should be measured twice weekly for 2-6 weeks following dose increases. In patients with CRF not on dialysis, the maintenance dose must also be individualized. PROCRIT doses of 75-150 Units/kg per week have been shown to maintain hematocrits of 36–38% for up to 6 months.

Delayed or Diminished Response: Over 95% of patients with CRF responded with clinically significant increases in hematocrit, and virtually all patients were transfusion-independent within approximately two months of initiation of PROCRIT therapy.

If a patient fails to respond or maintain a response, other etiologies should be considered and evaluated as clinically indicated. (See "PRECAUTIONS" section for discussion of

Starting Dose	Reduce Dose If	Increase Dose When	Maintenance Dose	Suggested Hct. Range
50-100 Units/kg T.I.W.; IV or SC	1) Hct. approaches 36%, or 2) Hct. increases > 4 points in any 2-week period	Hct. does not increase by 5-6 points after 8 weeks of therapy, and hct. is below suggested target range	Individually titrate	30-36%

Zidovudine-treated HIV-infected Patients

Prior to beginning PROCRIT, it is recommended that the endogenous serum erythropoietin level be determined (prior to transfusion). Available evidence suggests that patients receiving zidovudine with endogenous serum erythropoietin levels > 500 mUnits/mL are unlikely to respond to therapy with PROCRIT.

Starting Dose: For patients with serum erythropoietin levels ≤ 500 mUnits/mL who are receiving a dose of zidovudine ≤ 4,200 mg/week, the recommended starting dose of PROCRIT is 100 Units/kg as an intravenous or subcutaneous injection three times weekly (T.I.W.) for 8 weeks.

Increase Dose: During the dose adjustment phase of therapy, the hematocrit should be monitored weekly. If the response is not satisfactory in terms of reducing transfusion requirements or increasing hematocrit after 8 weeks of therapy, the dose of PROCRIT can be increased by 50-100 Units/kg (T.I.W.). Response should be evaluated every 4-8 weeks thereafter and the dose adjusted accordingly by 50-100 Units/kg increments (T.I.W.). If patients have not responded satisfactorily to a PROCRIT dose of 300 Units/kg (T.I.W.), it is unlikely that they will respond to higher doses of PROCRIT.

Maintenance Dose: After attainment of the desired response (i.e., reduced transfusion requirements or increased hematocrit), the dose of PROCRIT should be titrated to maintain the response based on factors such as variations in zidovudine dose and the presence of intercurrent infectious or inflammatory episodes. If the hematocrit exceeds 40%, the dose should be discontinued until the hematocrit drops to 36%. The dose should be reduced by 25% when treatment is resumed and then titrated to maintain the desired hematocrit.

Cancer Patients on Chemotherapy

Baseline endogenous serum erythropoietin levels varied among patients in these trials with approximately 75% (N=83/110) having endogenous serum erythropoietin levels < 132 mUnits/mL, and approximately 4% (N=4/110) of patients having endogenous serum erythropoietin levels > 500 mUnits/mL. In general, patients with lower baseline serum erythropoietin levels responded more vigorously to PROCRIT than patients with higher erythropoietin levels. Although no specific serum erythropoietin level can be stipulated above which patients would be unlikely to respond to PROCRIT therapy, treatment of patients with grossly elevated serum erythropoietin levels (e.g., > 200 mUnits/mL) is not recommended. The hematocrit should be monitored on a weekly basis in patients receiving PROCRIT therapy until hematocrit becomes stable.

Starting Dose: The recommended starting dose of PROCRIT is 150 Units/kg subcutaneously (T.I.W.).

Dose Adjustment: If the response is not satisfactory in terms of reducing transfusion requirements or increasing hematocrit after 8 weeks of therapy, the dose of PROCRIT can be increased up to 300 Units/kg (T.I.W.). If patients have not responded satisfactorily to a PROCRIT dose of 300 Units/kg (T.I.W.), it is unlikely that they will respond to higher doses of PROCRIT. If the hematocrit exceeds 40%, the dose of PROCRIT should be withheld until the hematocrit falls to 36%. The dose of PROCRIT should be reduced by 25% when treatment is resumed and titrated to maintain the desired hematocrit. If the initial dose of PROCRIT includes a very rapid hematocrit response (e.g., an increase of more than 4 percentage points in any 2-week period), the dose of PROCRIT should be reduced.

Surgery Patients

Prior to initiating treatment with PROCRIT a hemoglobin should be obtained to establish that it is >10 to ≤13 g/dL.[14] The recommended dose of PROCRIT is 300 U/kg/day subcutaneously for 10 days before surgery, on the day of surgery, and for 4 days after surgery.[14]

An alternate dose schedule is 600 U/kg PROCRIT subcutaneously in once weekly doses (21, 14 and 7 days before surgery) plus a fourth dose on day of surgery.[15]

All patients should receive adequate iron supplementation. Iron supplementation should be initiated no later than the beginning of treatment with PROCRIT and should continue throughout the course of therapy.

PREPARATION AND ADMINISTRATION OF PROCRIT

1. DO NOT SHAKE. It is not necessary to shake PROCRIT. Prolonged vigorous shaking may denature any glycoprotein, rendering it biologically inactive.
2. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use any vials exhibiting particulate matter or discoloration.
3. Using aseptic techniques, attach a sterile needle to a sterile syringe. Remove the flip-top from the vial of PROCRIT, and wipe the septum with a disinfectant. Insert the needle into the vial, and withdraw into the syringe an appropriate volume of solution.
4. **Single-dose** 1 mL vial contains no preservative. Use one dose per vial; do not re-enter vial. Discard unused portions. **Multidose** 1 mL and 2 mL vials contain preservative. Store at 2 to 8°C after initial entry and between doses. Discard 21 days after initial entry.
5. Do not dilute or administer in conjunction with other drug solutions. However, at the time of subcutaneous administration, preservative-free PROCRIT from single-use vials may be admixed in a syringe with bacteriostatic 0.9% sodium chloride injection, USP, with benzyl alcohol 0.9% (bacteriostatic saline) at a 1:1 ratio using aseptic technique. The benzyl alcohol in the bacteriostatic saline acts as a local anesthetic which may ameliorate subcutaneous injection site discomfort. Admixing is not necessary when using the multidose vials of PROCRIT containing benzyl alcohol.

HOW SUPPLIED

PROCRIT, containing Epoetin alfa, is available in vials containing color coded labels.

1 mL Single-Dose, Preservative-Free Solution

Each dosage form is supplied in the following packages:

Cartons containing six (6) **single-dose** vials:
- 2,000 Units/mL (NDC 59676-302-01) (Purple)
- 3,000 Units/mL (NDC 59676-303-01) (Magenta)
- 4,000 Units/mL (NDC 59676-304-01) (Green)
- 10,000 Units/mL (NDC 59676-310-01) (Red)

Cartons containing four (4) **single-dose** vials:
- 40,000 Units/mL (NDC 59676-340-01) (Orange)

Trays containing twenty-five (25) **single-dose** vials:
- 2,000 Units/mL (NDC 59676-302-02) (Purple)
- 3,000 Units/mL (NDC 59676-303-02) (Magenta)
- 4,000 Units/mL (NDC 59676-304-02) (Green)
- 10,000 Units/mL (NDC 59676-310-02) (Red)

2 mL Multidose, Preserved Solution

Cartons containing six (6) **multidose** vials:
- 10,000 Units/mL (NDC 59676-312-01) (Blue)

1 mL Multidose, Preserved Solution

Cartons containing six (6) **multidose** vials:
- 20,000 Units/mL (NDC 59676-320-01) (Lime)

STORAGE

Store at 2° to 8° C (36° to 46° F). Do not freeze or shake.

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PROCRIT®
EPOETIN ALFA

INFORMATION FOR HOME DIALYSIS PATIENTS

What is PROCRIT and how does it work?

PROCRIT is a copy of human erythropoietin, a hormone produced primarily by healthy kidneys. PROCRIT replaces the erythropoietin that the failed kidneys can no longer produce, and signals the bone marrow to make the oxygen-carrying red blood cells once again. PROCRIT is produced in mammalian cells that have been genetically altered by the addition of a gene of the natural substance erythropoietin.

How should I take PROCRIT?

In those situations where your doctor has determined that you, as a home dialysis patient, can self-administer PROCRIT, you will receive instruction on how much PROCRIT to use, how to inject it, how often you should inject it, and how you should dispose of the unused portions of each vial.

You will be instructed to monitor your blood pressure carefully everyday and to report any changes outside of the guidelines that your doctor has given you. When the number of red blood cells increases, your blood pressure can also increase, so your doctor may prescribe some new or additional blood pressure medication. Be sure to follow your doctor's orders. You may also be instructed to have certain laboratory tests, such as additional hematocrit or iron level measurements, done more frequently. You may be asked to report these tests to your doctor or dialysis center. Also, your doctor may prescribe additional iron for you to take. Be

Continue to check your access, as your doctor or nurse has shown you, to make sure it is working. Be sure to let your health care professional know right away if there is a problem.

Allergy to PROCRIT

Patients occasionally experience redness, swelling, or itching at the site of injection of PROCRIT. This may indicate an allergy to the components of PROCRIT, or it may indicate a local reaction. If you have a local reaction, consult your doctor. A potentially more serious reaction would be a generalized allergy to PROCRIT, which could cause a rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases of generalized allergy may be life-threatening. If you think you are having a generalized allergic reaction, stop taking PROCRIT and notify a doctor or emergency medical personnel immediately.

How will I know if PROCRIT is working?

The effectiveness of PROCRIT is measured by the increase in hematocrit (the amount of red blood cells in the blood) that results from PROCRIT therapy. The rise in hematocrit is not immediate. It usually takes about 2-6 weeks before the hematocrit starts to rise. The amount of time it takes, and the dose of PROCRIT that is needed to make the hematocrit increase, varies from patient to patient.

What is the most important information I should know about PROCRIT and CHRONIC RENAL FAILURE?

PROCRIT has been prescribed for you by your doctor because you:

1. Have anemia due to your kidney disease.
2. Are able to dialyze at home.
3. Have been determined to be able to administer PROCRIT without direct medical or other supervision.

A lack of energy or feeling of tiredness is the major symptom of anemia. Additional symptoms include shortness of breath, chest pain, and feeling cold all the time. The reason for these symptoms is that there is a lack of red blood cells. Red blood cells carry oxygen, which is important for all of the body's functions. When there are fewer red blood cells, the body does not get all the oxygen it needs.

Kidneys remove toxins from the blood; they also measure the amount of oxygen in the blood. If there is not enough oxygen, the kidneys will produce a hormone called erythropoietin. Erythropoietin is released into the bloodstream and travels to the bone marrow where red blood cells are made. Erythropoietin signals the bone marrow to make more oxygen-carrying red blood cells.

As the kidneys fail, they stop cleansing toxins from your blood. They also make less erythropoietin than they should. Therefore, the bone marrow does not receive a strong-enough signal to make the oxygen-carrying red blood cells. Fewer red blood cells are produced so the muscles, brain, and other parts of the body do not get the oxygen they need to function properly.

Most patients treated with PROCRIT no longer need blood transfusions. However, certain medical conditions, or unexpected blood loss, may result in the need for a transfusion.

What do I need to know if I am giving myself PROCRIT injections?

When you receive your PROCRIT from the dialysis center, doctor's office or home dialysis supplier, always check to see that:

1. The name PROCRIT appears on the carton and vial label.
2. You will be able to use PROCRIT before the expiration date stamped on the package.

The PROCRIT solution in the vial should always be clear and colorless. Do not use PROCRIT if the contents of the vial appear discolored or cloudy, or if the vial appears to contain lumps, flakes, or particles. In addition, if the vial has been shaken vigorously, the solution may appear to be frothy and should not be used. Therefore, care should be taken not to shake the PROCRIT vial vigorously before use.

Unless you have been prescribed Multidose PROCRIT (1 mL or 2 mL vials with a big "M" on the label, each containing a total of 20,000 Units of PROCRIT), vials of PROCRIT are for single use. Any unused portion of a vial should not be used. However, Multidose PROCRIT may be stored in the refrigerator between doses for up to 21 days, and can be used for multiple doses. Follow your dialysis center's instructions on what to do with the used vials.

How should I store PROCRIT?

PROCRIT should be stored in the refrigerator, but not in the freezing compartment. Do not let the vial freeze and do not leave it in direct sunlight. Do not use a vial of PROCRIT that has been frozen or after the expiration date that is stamped on the label. If you have any questions about the safety of a vial of PROCRIT that has been subjected to temperature extremes, be sure to check with your dialysis unit staff.

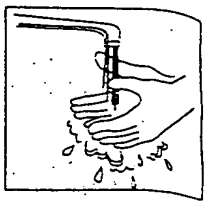
Always use the correct syringe.

Your doctor has instructed you on how to give yourself the correct dosage of PROCRIT. This dosage will usually be measured in Units per milliliter or cc's. It is important to use a syringe that is marked in tenths of milliliters (for example, 0.2 mL or cc). Failure to use the proper syringe can lead to a mistake in dosage, and you may receive too much or too little PROCRIT. Too little PROCRIT may not be effective in increasing your hematocrit, and too much PROCRIT may lead to a hematocrit that is too high. Only use disposable syringes and needles as they do not require sterilization; they should be used once and discarded after instructed

IMPORTANT: TO HELP AVOID CONTAMINATION AND POSSIBLE INFECTION, FOLLOW THESE INSTRUCTIONS EXACTLY.

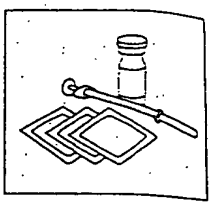
PREPARING THE DOSE

1. Wash your hands thoroughly with soap and water before preparing the medication.

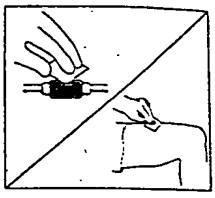


2. Check the date on the PROCRIT vial to be sure that the drug has not expired.

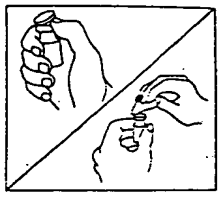
3. Remove the vial of PROCRIT from the refrigerator and allow it to reach room temperature. Each PROCRIT vial is designed to be used only once; do not reenter the vial. It is not necessary to shake PROCRIT. Prolonged vigorous shaking may damage the product. Assemble the other supplies you will need for your injection.



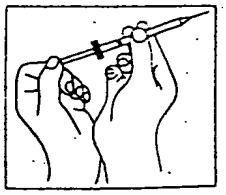
4. Hemodialysis patients should wipe off the venous port of the hemodialysis tubing with an antiseptic swab. Peritoneal dialysis patients should cleanse the skin with an antiseptic swab where the injection is to be made.



5. Flip off the red protective cap but do not remove the gray rubber stopper. Wipe the top of the gray rubber stopper with an antiseptic swab.

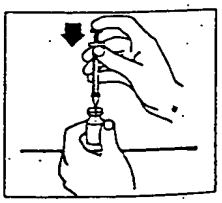


6. Using a syringe and needle designed for subcutaneous injection, draw air into the syringe by pulling back on the plunger. The amount of air should be equal to your PROCRIT dose.

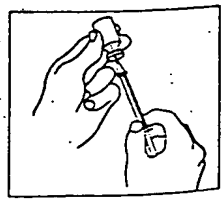


7. Carefully remove the needle cover. Put the needle through the gray rubber stopper of the PROCRIT vial.

8. Push the plunger in to discharge air into the vial. The air injected into the vial will allow PROCRIT to be easily withdrawn into the syringe.



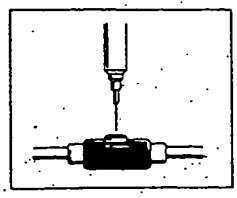
9. Turn the vial and syringe upside down in one hand. Be sure the tip of the needle is in the PROCRIT solution. Your other hand will be free to move the plunger. Draw back on the plunger slowly to draw the correct dose of PROCRIT into the syringe.



10. Check for air bubbles. The air is harmless, but too large an air bubble will reduce the PROCRIT dose. To remove air bubbles, gently tap the syringe to move the air bubbles to the top of the syringe, then use the plunger to push the solution and the air back into the vial. Then remeasure your correct dose of PROCRIT.

11. Double check your dose. Remove the needle from the vial. Do not lay the syringe down or allow the needle to touch anything.

INJECTING THE DOSE

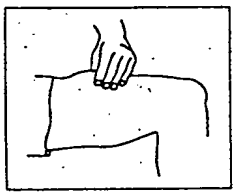


1. Insert the needle of the syringe into the previously cleansed venous port and inject the PROCRIT.

2. Remove the syringe and dispose of the whole unit. Use the disposable syringe only once. Dispose of syringes and needles as directed by your doctor, by following these simple steps:

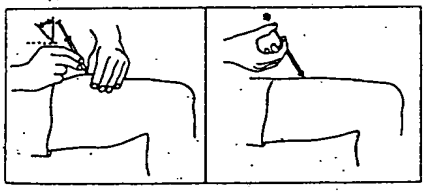
- Place all used needles and syringes in a hard plastic container with a screw-on-cap, or a metal container with a plastic lid, such as a coffee can properly labeled as to content. If a metal container is used, cut a small hole in the plastic lid and tape the lid to the metal container. If a hard-plastic container is used, always screw the cap on tightly after each use. When the container is full, tape around the cap or lid, and dispose of according to your doctor's instructions.
- Do not use glass or clear plastic containers, or any container that will be recycled or returned to a store.
- Always store the container out of the reach of children.
- Please check with your doctor, nurse, or pharmacist for other suggestions. There may be special state and local laws that they will discuss with you.

Patients on home peritoneal dialysis or home hemodialysis using the subcutaneous route:



1. With one hand, stabilize the previously cleansed skin by spreading it or by pinching up a large area with your free hand.

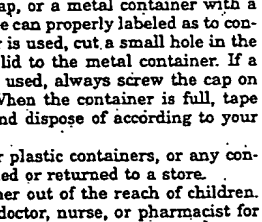
2. Hold the syringe with the other hand, as you would a pencil. Double check that the correct amount of PROCRIT is in the syringe. Insert the needle straight into the skin (90 degree angle). Pull the plunger back slightly. If blood comes into the syringe, do not inject PROCRIT, as the needle has entered a blood vessel; withdraw the syringe and inject at a different site. Inject the PROCRIT by pushing the plunger all the way down.



3. Hold an antiseptic swab near the needle and pull the needle straight out of the skin. Press the antiseptic swab over the injection site for several seconds.

4. **Use the disposable syringe only once.** Dispose of syringes and needles as directed by your doctor, by following these simple steps:

- Place all used needles and syringes in a hard plastic container with a screw-on-cap, or a metal container with a plastic lid, such as a coffee can properly labeled as to content. If a metal container is used, cut a small hole in the plastic lid and tape the lid to the metal container. If a hard-plastic container is used, always screw the cap on tightly after each use. When the container is full, tape around the cap or lid, and dispose of according to your doctor's instructions.
- Do not use glass or clear plastic containers, or any container that will be recycled or returned to a store.
- Always store the container out of the reach of children.
- Please check with your doctor, nurse, or pharmacist for other suggestions. There may be special state and local laws that they will discuss with you.



5. Always change the site for each injection as directed. Occasionally a problem may develop at the injection site. If you notice a lump, swelling, or bruising that doesn't go away, contact your doctor. You may wish to record the site just used so that you can keep track.

USAGE IN PREGNANCY

If you are pregnant or nursing a baby, consult your doctor before using PROCRIT.

IMPORTANT NOTES

Since you are a home dialysis patient and your doctor allows you to self-administer PROCRIT, please note the following:

1. Always follow the instructions of your doctor concerning the dosage and administration of PROCRIT. Do not change the dose or instructions for administration of PROCRIT without consulting your doctor.

2. Your doctor will tell you what to do if you miss a dose of [illegible]

3. Always consult your doctor if you notice anything unusual about your condition or your use of PROCRIT.

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Revised December 1998 638-29-979-5
6300G017

Shown in Product Identification Guide, page 328

SORANOX®

[spôr-a'nŏx]
(itraconazole) INJECTION

℞

WARNING: Coadministration of terfenadine, astemizole, and cisapride with SPORANOX® (itraconazole) Capsules, Oral Solution or Injection is contraindicated. SPORANOX® is a potent inhibitor of the cytochrome P450 3A4 enzyme system and may raise plasma concentrations of drugs metabolized by this pathway. Serious cardiovascular events, including death, ventricular tachycardia, and torsades de pointes have occurred in patients taking itraconazole concomitantly with terfenadine or cisapride, which are metabolized by the cytochrome P450 3A4 system. See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS: Drug Interactions for more information.

DESCRIPTION

For intravenous infusion (NOT FOR IV BOLUS INJECTION)

SPORANOX® is the brand name for itraconazole, a synthetic triazole antifungal agent. Itraconazole is a 1:1:1:1 racemic mixture of four diastereomers (two enantiomeric pairs), each possessing three chiral centers. It may be represented by the following structural formula and nomenclature:

(±)-1-[(R*)-sec-butyl]-4-[p-[4-[p[[(2R*,4S*)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ²-1,2,4-triazolin-5-one mixture with (±)-1-[(R*)-sec-butyl]-4-[p-[4-[p[[2S*,4R*)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]-
phenyl]-Δ²-1,2,4-triazolin-5-one

or

(±)-1-[(RS*)-sec-butyl]-4-[p-[4-[p[[(2R*,4S)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ²-1,2,4-triazolin-5-one

Itraconazole has a molecular formula of $C_{35}H_{38}Cl_2N_8O_4$ and a molecular weight of 705.64. It is a white to slightly yellowish powder. It is insoluble in water, very slightly soluble in alcohols, and freely soluble in dichloromethane. It has a pKa of 3.70 (based on extrapolation of values obtained from methanolic solutions) and a log (n-octanol/water) partition coefficient of 5.66 at pH 8.1.

SPORANOX® (itraconazole) Injection is a sterile pyrogen-free clear, colorless to slightly yellow solution for intravenous infusion. Each mL contains 10 mg of itraconazole, solubilized by hydroxypropyl-β-cyclodextrin (400 mg) as a molecular inclusion complex, with 3.8 µL hydrochloric acid, 25 µL propylene glycol, and sodium hydroxide for pH adjustment to 4.5, in water for injection. SPORANOX® Injection is packaged in 25 mL colorless glass ampules, containing 250 mg of itraconazole, contents of which are diluted in 50 mL 0.9% Sodium Chloride Injection, USP (Normal Saline) prior to infusion. When properly administered, contents of one ampule will supply 200 mg of itraconazole.

CLINICAL PHARMACOLOGY

Pharmacokinetics and Metabolism: NOTE: The plasma concentrations reported below were measured by high performance liquid chromatography (HPLC) specific for itraconazole. When itraconazole in plasma is measured by a bioassay, values reported may be higher than those obtained by HPLC due to the presence of the bioactive metabolite, hydroxyitraconazole. (See MICROBIOLOGY.)

The pharmacokinetics of SPORANOX® (itraconazole) Injection (200 mg b.i.d. for two days, then 200 mg q.d. for five days) followed by oral dosing of SPORANOX® Capsules were studied in patients with advanced HIV infection. Steady-state plasma concentrations were reached after the fourth dose for itraconazole and by the seventh dose for hydroxyitraconazole. Steady-state plasma concentrations were maintained by administration of SPORANOX Capsules, 200 mg b.i.d. Pharmacokinetic parameters for itraconazole and hydroxyitraconazole are presented in the table below: [See table below]

The estimated mean ±SD half-life at steady state of itraconazole after intravenous infusion was 35.4 ± 29.4 hours. In previous studies, the mean elimination half-life for itraconazole at steady state after daily oral administration of 100 to 400 mg was 30–40 hours. Approximately 93–101% of hydroxypropyl-β-cyclodextrin was excreted unchanged in the urine within 12 hours after dosing.

The plasma protein binding of itraconazole is 99.8% and that of hydroxyitraconazole is 99.5%. Following intravenous administration, the volume of distribution of itraconazole averaged 796 ± 185 L.

Itraconazole is extensively metabolized resulting in the formation of several metabolites including hydroxyitraconazole, the major metabolite. Results of a pharmacokinetics study suggest that itraconazole may undergo saturable metabolism with multiple dosing. Fecal excretion of the parent drug varies between 3–18% of the dose. Renal excretion of the parent drug is less than 0.03% of the dose. About 40% of the dose is excreted as inactive metabolites in the urine. No single excreted metabolite represents more than 5% of a dose. Itraconazole total plasma clearance averaged 381 ± 95 mL/min following intravenous administration. Approximately 80–90% of hydroxypropyl-β-cyclodextrin is eliminated through the kidneys.

Special populations:

Renal Insufficiency: Plasma concentrations of itraconazole in patients with mild to moderate renal insufficiency were comparable to those obtained in healthy subjects. The majority of the 8-gram dose of hydroxypropyl-β-cyclodextrin was eliminated in the urine during the 120-hour collection period in normal subjects and in patients with mild to severe renal insufficiency. Following a single intravenous dose of 200 mg to subjects with severe renal impairment (creatinine clearance ≤ 19 mL/minute), clearance of hydroxypropyl-β-cyclodextrin was reduced six-fold compared with subjects with normal renal function. SPORANOX® Injection should not be used in patients with creatinine clearance < 30 mL/min.

Hepatic Insufficiency: The effect of hepatic impairment on plasma concentrations of itraconazole is unknown. It is recommended that patients with hepatic impairment be carefully monitored when taking itraconazole.

MICROBIOLOGY

Mechanism of Action: *In vitro* studies have demonstrated that itraconazole inhibits the cytochrome P-450-dependent synthesis of ergosterol, which is a vital component of fungal cell membranes.

Activity in vitro and in vivo: Itraconazole exhibits *in vitro* activity against *Blastomyces dermatitidis, Histoplasma capsulatum, Histoplasma duboisii, Aspergillus flavus, Aspergillus fumigatus, Candida albicans* and *Cryptococcus neoformans.* Itraconazole also exhibits varying *in vitro* activity against *Sporothrix schenckii,* Trichophyton spp., *Candida krusei* and other Candida spp. The bioactive metabolite, hydroxyitraconazole, has not been evaluated against *Histoplasma capsulatum* and *Blastomyces dermatitidis.* Correlation between *in vitro* minimum inhibitory concentration (MIC) results and clinical outcome has yet to be established for azole antifungal agents.

Itraconazole administered orally was active in a variety of animal models of fungal infection using standard laboratory strains of fungi. Fungistatic activity has been demonstrated against disseminated fungal infections caused by *Blastomyces dermatitidis, Histoplasma duboisii, Aspergillus fumigatus, Coccidioides immitis, Cryptococcus neoformans, Paracoccidioides brasiliensis, Sporothrix schenckii, Trichophyton rubrum* and *Trichophyton mentagrophytes.*

Itraconazole administered at 2.5 mg/kg and 5.0 mg/kg via the oral and parenteral routes increased survival rates and sterilized organ systems in normal and immunosuppressed guinea pigs with disseminated *Aspergillus fumigatus* infections. Oral itraconazole administered daily at 40 mg/kg and 80 mg/kg increased survival rates in normal rabbits with disseminated disease and immunosuppressed rats with pulmonary *Aspergillus fumigatus* infection, respectively. Itraconazole has demonstrated antifungal activity in a variety of animal models infected with *Candida albicans* and other Candida species.

Resistance: Isolates from several fungal species with decreased susceptibility to itraconazole have been isolated *in vitro* and from patients receiving prolonged therapy.

Several *in vitro* studies have reported that some fungal clinical isolates, including Candida species, with reduced susceptibility to one azole antifungal agent may also be less susceptible to other azole derivatives. The finding of cross-resistance is dependent upon a number of factors; including the species evaluated, its clinical history, the particular

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Parameter	Injection Day 7 n = 29		Capsules, 200 mg b.i.d. Day 36 n = 12	
	itraconazole	hydroxyitraconazole	itraconazole	hydroxyitraconazole
C_{max} (ng/mL)	2856 ± 866*	1906 ± 612	2010 ± 1420	2614 ± 1703
t_{max} (hr)	1.08 ± 0.14	8.53 ± 6.36	3.92 ± 1.83	5.92 ± 6.14
AUC_{0-12h} (ng·h/mL)	—	—	18768 ± 13933	28516 ± 19149
AUC_{0-24h} (ng·h/mL)	30605 ± 8961	42445 ± 13282	—	—